RESTRICTED

WHO Collaborating Centre for International Drug Monitoring

SIGNAL

Analyses of reports in the WHO global database of individual case safety reports, VigiBase • April 2017

Signals in this issue

- Ivermectin – Serious neurological events
- Ruxolitinib – Peripheral neuropathy

Interaction signals

- Ciprofloxacin and enalapril – Acute kidney injury
- Rosuvastatin and ticagrelor – Rhabdomyolysis

Paediatric signal

- Desloratadine, loratadine – Weight increase

Uppsala Monitoring Centre

Please direct all correspondence regarding signals presented in this document to Uppsala Monitoring Centre

SIGNAL

WHO defines a signal as:
"Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously". An additional note states: "Usually more than one report is required to generate a signal, depending on the seriousness of the event and the quality of the information".*

A signal is therefore a hypothesis together with supporting data and arguments. A signal is not only uncertain but also preliminary in nature: the situation may change substantially over time one way or another as more information is gathered. A signal may also provide further documentation of a known association of a drug with an ADR, for example: information on the range of severity of the reaction; the outcome; postulating a mechanism; indicating an "at risk" group; a dose range which might be more suspect; or suggesting a pharmaceutical group effect or a lack of such an effect by a particular drug.

SIGNAL is edited and produced by UMC and presents signals derived from VigiBase, the WHO global database of individual case safety reports. This database contains summaries of individual case safety reports of suspected adverse drug reactions, submitted by national pharmacovigilance centres (NCs) that are members of the WHO Programme for International Drug Monitoring. More information regarding the status of this data, its limitations and proper use, is provided in the Caveat on the last page of this document.

VigiBase is periodically screened to identify drug-ADR combinations that are unknown or incompletely documented. Combinations of such interest that they should be further reviewed clinically are sent to members of the Signal Review Panel for in-depth assessment. The Signal Review Panel consists of experienced international scientists and clinicians, usually affiliated with a governmental or an academic institution. The expert investigates the clinical evidence for the reaction being related to the suspected drug.

The topics discussed in SIGNAL represent varying levels of suspicion. SIGNAL contains hypotheses, primarily intended as information for the national regulatory authorities. They may consider the need for possible action, such as further evaluation of source data, or conducting a study for testing a hypothesis.

The distribution of SIGNAL is currently restricted to NCs, regulatory authority staff and their advisers, participating in the WHO Programme. Excerpts of SIGNAL are sent to the pharmaceutical companies when they can be identified as uniquely responsible for the drug concerned. UMC does not take responsibility for contacting all market authorisation holders. As a step towards increased transparency, since 2012 UMC signals are subsequently published in the *WHO Pharmaceuticals Newsletter*.

National regulatory authorities and NCs are responsible for deciding on action in their countries, including communicating the information to health professionals, and the responsible market authorisation holders, within their jurisdiction.

In order to further debate, we encourage all recipients of SIGNAL to comment on individual topics.

** Edwards I.R, Biriell C. Harmonisation in pharmacovigilance. Drug Safety 1994;10:93-102.*

Content of SIGNAL April 2017

Source information

IMS LifeCycle has been used as a source of information regarding the licensor/patent holders, to which certain signals have been submitted for comments.

Responses from industry

Responses from industry are unedited. The calculations, analysis and conclusions are theirs, and should be given serious but critical consideration in the same way as any scientific document. The WHO and UMC are not responsible for their findings, but may occasionally comment on them.

Editorial team

Pia Caduff-Janosa, Jenny Hartman, Sara Hult, Lovisa Sandberg, Sarah Watson, Camilla Westerberg.

Editorial

Ruth Savage, Uppsala Monitoring Centre and New Zealand

This second issue of SIGNAL for 2017 includes five signals from a recent screening of VigiBase for drug-drug interactions as well as signals generated from previous subgroup and standard screenings. The recent screening used a drug-drug interaction algorithm[1] for the first time in routine signal detection. Rosuvastatin, ticagrelor and rhabdomyolysis is a suspected interaction with an unclear mechanism. Several potential contributors such as rosuvastatin dose, alterations in renal function and transporter activity are considered. Given the seriousness of the suspected interaction it will be important to observe if the signal is confirmed and a mechanism found. Ciprofloxacin, enalapril and acute kidney injury is a signal strengthening report since there is one publication of a similar finding. Readers may find it helpful to refer to the inside back cover for a brief guide to the interpretation of the UMC Measures of Disproportionate Reporting of drug-drug-ADR triplets as well as the more familiar measures for drug-ADR pairs.

The signal desloratadine, loratadine and weight increase comes from the paediatric screening with its focus on reports for children, and ivermectin and serious neurological events from the regional screening which focused on reports from Africa, Asia and Latin America and the Caribbean. Lastly, from the most recent standard screening of VigiBase, with a primary focus on serious adverse reactions for new drugs on the market, we have ruxolitinib and peripheral neuropathy.

One effect of the interaction screening was that it highlighted issues of report quality. Low quality reports initially made the combinations difficult to assess. Frequently there were no dates and no narrative information which made evaluation of drug-drug interactions particularly difficult. This meant that a new filter had to be added so that drug-drug-ADR combinations were assessed only if they contained at least three reports with narratives.

Report quality is an issue which we must grapple with and National Centres have a key role. Pharmacovigilance databases remain the mainstay of identifying serious unexpected reactions despite endeavours to find other sources. However, our ability to publish well-documented alerts promptly from international data could be improved enormously with more complete reports together with narratives. These would be handled with care and give back to the system important signals. If report data is too incomplete, strong suspicions of serious reactions detected in VigiBase are considered unsound and cannot be published and acted upon. All the details we request in the reports are important as variables that can influence our assessments including patient demographics, disease history, renal, hepatic and pregnancy status, drug administration dates and indications. In addition, narrative space is an opportunity for reporters to include their clinical reasoning and support for the diagnoses they have made which may be crucial to the interpretation of a report. It also allows patients to relate their experiences. Professor Ralph Edwards in a recent publication about the continuing challenge of causality assessment has emphasised the importance of clinical details to identify patients at risk and prevent or limit harmful outcomes.[2]

Of course reports even with narrative are not always useful. They may lack key details or have uninformative narrative. How can we encourage more detailed and thoughtful information from reporters without discouraging reporting altogether? The challenge is for each country to create its own strategies and share those that are successful with others.

References

1. Strandell J, Caster O, Hopstadius J, Edwards IR, Norén GN. The development and evaluation of triage algorithms for early discovery of adverse drug interactions. Drug Saf. 2013 May;36(5):371-88.
2. Edwards IR. Causality assessment in pharmacovigilance: still a challenge. Drug Saf. 2017 [Epub ahead of print]

Ciprofloxacin, enalapril and acute kidney injury: strengthening of a drug interaction signal

Ruth Savage, Uppsala Monitoring Centre and New Zealand

Summary

A case series of 16 reports in VigiBase, the WHO global database of individual case safety reports, of acute kidney injury (AKI) associated with enalapril and ciprofloxacin as co-suspect or interacting medicines was identified through statistical screening for suspected drug interactions. The suspected interaction is unlabelled. Use of enalapril, an angiotensin converting enzyme (ACE) inhibitor, may lead to renal impairment due to altered renal haemodynamics in particular clinical situations or with other medicines that affect renal glomerular filtration. Increased serum creatinine and blood urea nitrogen have been observed in ciprofloxacin users and AKI has been reported in approximately 1 in 1,500 patients. Clinical assessment of the VigiBase reports identified 11 patients for whom a direct renal effect of ciprofloxacin alone or interacting with enalapril was the most likely explanation for AKI. In the remaining five reports an alternative explanation was more likely. Most of the patients in the 11 reports that supported causality had characteristics that increased their risk of renal failure, including patients aged over 80 years with two or more risk factors for ACE inhibitor-related renal failure. Despite their high risk most patients did not develop AKI until ciprofloxacin was added to their regime. A nested case-control study in a cohort of older male patients admitted to hospital for AKI demonstrated a 2-fold greater risk for AKI with fluoroquinolones compared with no use and a 4.6-fold increase in risk for fluoroquinolones combined with renin-angiotensin blockers. This observation is in keeping with the VigiBase disproportionality measure for ciprofloxacin and enalapril.

The observed versus expected values for AKI with two other ACE inhibitors and ciprofloxacin as co-suspect or interacting also supported an ACE inhibitor class effect. There were insufficient reports to assess other fluoroquinolones.

Although the mechanism is unclear, three observations support this signal. The two statistical observations from the published case-control study and from VigiBase and, thirdly, the onset of AKI after ciprofloxacin was added to the regimes of patients taking enalapril most of whom were already at high risk of AKI. This signal suggests further investigation is needed to ascertain if there is an additional risk of nephrotoxicity with ciprofloxacin in patients taking an ACE inhibitor.

Introduction

A signal detection screening focusing on drug-drug interactions identified disproportionate reporting of a combination of ciprofloxacin, enalapril and acute kidney injury (AKI) in VigiBase, the WHO global database of individual case safety reports.

A range of pre-renal, renal and post-renal clinical conditions can lead to AKI. Drugs can be involved at any of these levels and so may cause conditions leading to pre-renal injury by volume depletion e.g. through haemorrhage or dehydration, or through a direct effect on glomerular arteriolar pressures. Drug-induced direct renal toxicity e.g. due to interstitial nephritis or acute tubular necrosis is well-recognised. Promotion of renal stone formation can lead to post-renal obstruction and AKI.

Ciprofloxacin is a broad spectrum fluoroquinolone antibiotic. It has been estimated that about 1 in 1,500 patients develop AKI after taking ciprofloxacin.[1] The underlying pathology identified through published case histories was interstitial nephritis in most patients.[2] There have also been reports of increased serum creatinine and blood urea nitrogen and, more rarely, crystalluria and macrohaematuria.[3] As a broad spectrum antibiotic, it can also cause diarrhoea which may lead to dehydration and AKI in susceptible patients.

Enalapril is an angiotensin converting enzyme (ACE) inhibitor used to reduce blood pressure and treat cardiac failure. ACE inhibitors decrease the production of angiotensin II, a substance which causes post-glomerular arteriolar constriction thus maintaining glomerular capillary filtration. Usually pre-glomerular arteriolar pressures are high enough for adequate filtration in the presence of ACE inhibition but drugs and clinical conditions that affect renal blood flow and pre-glomerular arteriolar pressures may trigger renal failure in patients taking ACE inhibitors. These include concomitant use of loop, thiazide or potassium-sparing diuretics, and prostaglandin inhibitors (NSAIDs), renal artery stenosis, renal transplant, old age, ischaemic heart disease and congestive heart failure, sodium restriction, sodium depletion, volume depletion, hypotension and gastrointestinal fluid loss.[4]

Reports in VigiBase

As of 14 September 2016, VigiBase holds 16 reports that include ciprofloxacin and enalapril as suspect or interacting medicines and the MedDRA preferred term acute kidney injury. At the time of the signal detection screening the number of reports in this combination was 15 with an expected number of only two. The UMC measure of disproportionate reporting for drug-drug interactions (Ω)[5] in VigiBase was 2.38 for Ω and 1.56 for the lower limit of the 95% credibility interval, Ω_{025}.

The 16 reports are from six countries, eight from Spain, two each from Italy, Switzerland and the United States (US), and one each from Germany and Sweden. No duplicates were detected.

Table 1 shows the report details. There were eight males and eight females. The age range was 42 to 97 years with a median of 77.5 years. Patient characteristics included background chronic renal failure (CRF) in six patients. The indication for ciprofloxacin was urinary tract infection, cystitis or prostatitis for eight patients, four of whom had CRF. The time to onset of AKI from commencement of ciprofloxacin, recorded for 13 patients, was 0 to 43 days with a median of 5.5 days. Most patients had taken ciprofloxacin for two weeks or less. The route of administration was oral (13 patients) and the daily dose (six patients) 500 or 1000 mg. For enalapril, complete administration dates were recorded for six patients, four were long term users and two short term. The patients in the remaining reports were also long term users with the start date unknown. The route of administration was oral (13 patients). Daily doses (eight patients) were within the recommended range of 2.5 to 20 mg, with one outlier taking 50 mg.

Assessment of individual case reports indicated a more likely alternative reason for AKI than a nephrotoxic effect of ciprofloxacin with enalapril in five patients (cases 12-16). These were dronedarone-related AKI (12), Lyell's syndrome attributed to allopurinol or, less likely, ciprofloxacin (13), sepsis, pancytopenia and AKI with multiple antibiotics (14), AKI after multiple antibiotics for chemotherapy-related infection (15), a combined effect of metamizole, an NSAID, added to furosemide and enalapril two days prior to AKI onset with ciprofloxacin commenced on the day of AKI onset (16).

Analysis of cases 1 to 11 in Table 1 indicated that in most patients although clinical conditions and a number of medicines were likely to have increased their risk of AKI, including ACE inhibitor-related AKI, the event did not occur until after a recent ciprofloxacin prescription lending weight to ciprofloxacin being the cause or a combined action of ciprofloxacin and enalapril.

Enalapril was used long term in nine patients and ciprofloxacin use was short term in all eleven. Co-suspect medicines with enalapril and ciprofloxacin were recorded in 10 of the 11 reports and included NSAIDs (2, 8) and diuretics (3, 4, 5, 6, 11). All but one case was recorded as serious. At least five patients were admitted and four had prolonged hospital stays. After suspect medicines were stopped, ten patients recovered or were recovering and one died of cardiac failure eight days later.

Three case reports (1, 7 and 10) are key reports. In case report 1 metformin was also suspect but it had been taken for two months and appears unlikely to have contributed. The patient in case report 7 had CRF and had taken bisoprolol, also suspect, for several months but renal impairment is not a labelled adverse drug reaction for this medicine. The patient recovered from AKI when all three medicines were discontinued. Patient 10 was also taking omeprazole, a known cause of interstitial nephritis, but he recovered when enalapril and ciprofloxacin were withdrawn and omeprazole continued.

In five case reports, recent commencement of a diuretic (4, 5) or an NSAID (8) or recent rather than long term prescription of enalapril with a diuretic (11) may have triggered enalapril-related AKI or contributed when ciprofloxacin was added. One of these patients (4) and two others (2, 6) had diarrhoea and/or vomiting which may have had a similar effect. It is theoretically possible that in case report 3 renal tubular inhibition of methotrexate excretion by ciprofloxacin led to renal failure.

An important feature of the 11 reports, with the exception of reports 1 and 10, is the patient characteristics that made them vulnerable to renal failure in association with enalapril use.[3] Seven patients were taking diuretics and two were taking NSAIDs, three had diarrhoea and/or vomiting and four had cardiac conditions. Five patients were aged over 80 years and it is of note that four of these very elderly patients had two or more risk factors in addition to their age for enalapril-related renal failure. Therefore, if there is a ciprofloxacin effect when taken with enalapril, it is most evident in very vulnerable patients.

If the AKI after ciprofloxacin was introduced could be entirely explained by infection or antibiotic-related diarrhoea, then disproportionate reporting would be expected for AKI with enalapril and other antibiotics. This disproportionality (Ω_{025} >0) was not observed with amoxicillin, azithromycin or flucloxacillin which, like ciprofloxacin, are used in an ambulatory setting (Table 2). The disproportionality measures do support a class effect of ACE inhibitors with ciprofloxacin (Ω_{025} >0). More evidence is needed to ascertain if there is a class effect for fluoroquinolones as there were few reports.

Literature and Labelling

The United Kingdom summary of product characteristics and US Food and Drug Administration (FDA) labels for enalapril (Innovace®, Vasotec®) and ciprofloxacin (Cipro®) do not list the two substances as interacting.[3,6,7,8] These labels reiterate the information about renal dysfunction with each of these medicines, described in the Introduction.

Lomaestro[2] conducted a literature review to ascertain the incidence and characteristics of fluoroquinolone-related nephrotoxicity. Publications were mostly case reports and the incidence was difficult to estimate. Nearly all of the 44 reports of acute renal failure identified involved patients aged over 50 years. The most frequently reported pathology was acute interstitial nephritis. A high proportion of patients were taking other nephrotoxic medicines, particularly chemotherapeutic and immunosuppressive agents. One patient was taking an ACE inhibitor.

A nested case-control study examined the risk of AKI with the use of fluoroquinolones in a cohort of men aged between 40 and 85 years in the US IMS Lifelink Heath Plan Claims Database.[1] The number of cases and controls was 1,292 and 12,651 respectively. After adjusting for fluoroquinolone indication, which included genitourinary infections, diseases associated with AKI including congestive heart failure and diabetes, and potentially nephrotoxic medicines with high use i.e. NSAIDs, loop diuretics and renin-angiotensin blockers, the rate ratio (RR) of AKI with current fluoroquinolone use was 2.18 (95% confidence interval (CI) 1.74 – 2.73), which equated to an absolute increase in AKI of 6.5/10,000 person-years or one additional case per 1,529 patients given a fluoroquinolone. This finding was supported by the results of a case-time-control analysis in the same cohort in which within-patient comparisons were made of drug exposures. The findings were similar whether or not patients had genitourinary infection or chronic kidney disease. The highest RR for the individual fluoroquinolones was for ciprofloxacin (2.76, 95% CI 2.03 – 3.76). This increased risk was not found with amoxicillin and azithromycin suggesting infection was not an alternative explanation.

The authors also hypothesised interactions between fluoroquinolones and NSAIDs, loop diuretics or renin-angiotensin system blockers (ACE inhibitors or angiotensin-receptor blockers) but only had sufficient power to examine the renin-angiotensin system blockers. There was no increase in risk of AKI with renin-angiotensin system blocker treatment alone (RR 1.00, 95% CI 0.84 – 1.18) but the combined use of these medicines with fluoroquinolones increased the RR for AKI from 2.18 for fluoroquinolones alone to 4.46 (95% CI 2.84 – 6.99) which was greater than the additive risk.

The lack of increased risk of AKI with renin-angiotensin system blockers alone was unexpected. The authors considered that physician monitoring of serum creatinine levels, particularly after starting renin-angiotensin blockers may be one explanation.

Discussion and Conclusion

The VigiBase case reports describe AKI occurring soon after ciprofloxacin was prescribed in patients taking enalapril. This adverse effect could be attributable to ciprofloxacin alone or to infection. However, three observations suggest a combined effect. Firstly, the increased disproportionality measure (Ω_{025} >0) for the enalapril/ciprofloxacin/AKI combination compared with the background data in VigiBase. Secondly, an independent nested case control study showed a greater than additive risk of AKI with co-prescribed fluoroquinolones and renin angiotensin blockers.[1] Thirdly, in the VigiBase reports a high proportion of patients were at risk of AKI including ACE inhibitor adverse renal effects, but AKI did not occur until ciprofloxacin was added.

While the contributing reports to the other combinations in Table 2 need more clinical assessment, the disproportionality measures suggest that infection and antibiotic-related diarrhoea do not completely explain the observations. In addition, the case-control study[1] suggested that urinary tract infection indications for ciprofloxacin were also unlikely to be an explanation. The disproportionality estimates in Table 2 do support a class effect of ACE inhibitors with ciprofloxacin.

Table 1. Characteristics of case reports in VigiBase of acute kidney injury (AKI) in association with ciprofloxacin and enalapril

Case	Age/Sex	Suspect (S) or interacting (I) drugs	Daily dose	Route	Time to onset of AKI	Indication	Concomitant medicines	Co-reported ADRs	Relevant medical history	Dechallenge, outcome	Comment
1	52/F	Enalapril, ciprofloxacin, metformin (all I)	50 mg 1000 mg 1700 mg	Oral Oral Oral	LT* 6 days 2 months	Hypertension UTI** T2DM***	Clonazepam	-	Hypertension, diabetes	All suspects discontinued, recovering	-
2	87/M	Enalapril, ciprofloxacin, ibuprofen, pravastatin (all I)	- - - -	Oral Oral Oral Oral	LT 5 days LT LT	Hypertension UTI - Hyperlipidaemia	Rivaroxaban, risperidone	Diarrhoea, speech and walking problems, blood glucose uncontrolled	CRF****, diarrhoea	All suspects discontinued, recovered	Profuse diarrhoea 2 days after starting ciprofloxacin
3	74/M	Enalapril, ciprofloxacin, metolazone, torasemide, methotrexate (all S)	20 mg - 5 mg/week 5 mg One dose weekly	Oral Oral Oral Oral SC	LT 12 days LT LT LT	- - - - -	Acenocoumarol, bisoprolol, glimepiride, metformin, simvastatin, deflazacort, pantoprazole, oxazepam	-	Septic arthritis, cardiomyopathy, T2DM, peripheral obliterating arteriopathy	All suspects discontinued, improved then relapsed. Metformin discontinued, recovering.	Abdominal sonography normal
4	94/F	Enalapril, ciprofloxacin, furosemide (all S)	5 mg - -	Oral Oral Oral	6 months 5 days 13 days	Hypertension Bronchitis Cardiac decompensation	Glyceryl trinitrate, folic acid, tiotropium, fluticasone/salmeterol, acetylsalicylic acid, lorazepam, colecalciferol, mirtazapine, omeprazole	Diarrhoea, vomiting, hyponatraemia	-	All suspects discontinued, recovering	-
5	61/M	Enalapril, ciprofloxacin, furosemide (all I)	- - -	Oral Oral Oral	7 days 7 days 7 days	Hypertension UTI Hypertension	-	Dehydration	Hypertension	All suspects discontinued, recovered	-
6	85/F	Enalapril, ciprofloxacin, hydrochlorothiazide (all I)	20 mg 1.0 g 12.5 mg	Oral Oral Oral	LT 6 days 2-3 months	Hypertension Bronchitis or gastroenteritis Hypertension	Metformin, trimetazidine, simvastatin, alprazolam, ipratropium, omeprazole	Nausea, vomiting, hypoxia, hypotension, tachycardia, tachypnoea	Hypertension, dyslipidaemia, T2DM, glaucoma, dizziness, acute bronchitis	All suspects discontinued, recovered	-
7	89/M	Enalapril, ciprofloxacin, bisoprolol (all I)	- - -	Oral Oral Oral	9-21 months 4 days 9-21 months	Hypertension Prostatitis -	Paracetamol, alprazolam, ranitidine	-	CRF	All medicines discontinued, recovered	-
8	62/M	Enalapril, ciprofloxacin, ibuprofen (all S)	- - -	- - -	LT 0-24 days 0-24 days	Hypertension UTI "Trouble with knee"	-	Serum creatinine 300 mmol/L	Hypertension 25 years treated with beta blocker, diuretic and ACE inhibitor. Unclear if first two current.	All suspects discontinued, recovering	Renal CT and ultrasound scan normal
9	86/M	Enalapril, ciprofloxacin, acetylsalicylic acid, amoxicillin/clavulanate (all I)	5 mg 1000 mg 300 mg -	Oral Oral Oral Oral	LT 4 days LT 4 days	Cardiomyopathy Bacterial respiratory infection Cardiomyopathy Bacterial respiratory infection	Furosemide, paracetamol	-	CRF	All medicines discontinued. Treated with frusemide and dopamine. Died.	Died due to cardiac failure 8 days after medicines were discontinued
10	63/M	Enalapril, ciprofloxacin (both I)	20 mg 1000 mg	Oral Oral	5-17 months 6 days	Hypertension UTI	Omeprazole, pentoxifylline	-	Hypertension	Both suspects discontinued, recovering	Renal artery stenosis on Doppler ECHO but arteriography normal

Case	Age/Sex	Suspect (S) or interacting (I) drugs	Daily dose	Route	Time to onset of AKI	Indication	Concomitant medicines	Co-reported ADRs	Relevant medical history	Dechallenge, outcome	Comment
11	73/M	Enalapril, ciprofloxacin, furosemide (all S)	2.5 mg 1000 mg 125 mg	Oral Oral Oral	5 days 11 days -	Heart disease complications Bronchopneumonia Heart disease complications	Triazolam, digoxin	-	-	All suspects discontinued, recovered	-
12	81/F	Enalapril, ciprofloxacin, dronedarone, sitagliptin, acenocoumarol (all S)	5 mg 500 mg 400 mg - -	Oral Oral Oral Oral Oral	- 43 days - - -	Hypertension Cystitis Atrial fibrillation T2DM Atrial fibrillation	Insulin	-	CRF, T2DM, bladder cancer, macrohaematuria	Sitagliptin and enalapril discontinued and vessel resection, no improvement. Dronedarone discontinued, recovering.	Conflicting information for ciprofloxacin discontinuation
13	83/F	Enalapril, ciprofloxacin, allopurinol, moxifloxacin (all S)	20 mg - 300 mg -	Oral Oral Oral IV	- 3 days - 0 days	- Infected scar - -	-	Lyell's syndrome or paraneoplastic syndrome	CRF, renal anaemia, hypertension, hyperuricaemia, adenocarcinoma, infected biopsy scar	All suspects discontinued, outcome unknown	-
14	54/F	Enalapril, ciprofloxacin, allopurinol, metformin, telavancin, cefepime, amoxicillin/clavulanate, ceftriaxone (all S)	- - - - - - - -	- - - - IV - - parenteral	- - - - 17 days - - 30 days	- - - - Osteomyelitis - - Diabetic foot	-	Klebsiella infection, diarrhoea, hypertensive heart disease, osteomyelitis, sepsis, pneumonia, cellulitis, tubulo-interstitial nephritis, pancytopenia	Hypertension, gout, dyslipidaemia, uncontrolled diabetes	All suspects discontinued, recovered	Leucopenia after telavancin and cefepime, then pancytopenia after all other antibiotics
15	42/F	Enalapril, ciprofloxacin, paclitaxel, carboplatin, oxacillin, vancomycin (all S)	- - 340 mg 703 mg - -	- - IV IV - -	- - 12 days 12 days - -	Hypertension Pneumonia NSCLC***** NSCLC Infection Pneumonia	-	Device-related infection, rash, pneumonia. Vancomycin trough level high at 34.9 (no units).	Hypertension, chronic obstructive pulmonary disease	Chemotherapy discontinued, no improvement. Other suspects discontinued, recovered.	Ramucirumab one month prior. Infection during chemotherapy. AKI and rash after start antibiotics.
16	97/F	Enalapril, ciprofloxacin, furosemide, metamizole (all I)	- - - -	Oral Oral Oral Oral	c. 2 years 0 days - 2 days	Hypertension UTI Cardiac failure Osteoarthritis	-	Serum creatinine 501 mmol/L	CRF, hypertension	Enalapril, ciprofloxacin and metamizole discontinued, recovered	-

**LT, drug administration assumed to be long term in a report where end date recorded and precise dates for short term drugs recorded in a report;*
***UTI, urinary tract infection;*
****T2DM, Type 2 diabetes mellitus;*
*****CRF, chronic renal failure;*
******NSCLC, non-small cell lung cancer.*

Table 2. Disproportionality statistics from VigiBase for combinations of acute kidney injury with (1) ciprofloxacin and ACE inhibitors (2) enalapril and a fluoroquinolone (3) enalapril and other antibiotics

Combination no.	Drug 1	Drug 2	Drug 2 status	N observed	N expected	Ω	Ω_{025}***
1	Ciprofloxacin	Enalapril	SI*	15	2	2.38	1.56
1	Ciprofloxacin	Enalapril	SIC**	61	30.7	0.93	0.55
1	Ciprofloxacin	Lisinopril	SI	10	3.8	1.30	0.27
1	Ciprofloxacin	Lisinopril	SIC	129	59.4	1.11	0.85
1	Ciprofloxacin	Ramipril	SI	13	3.2	1.88	0.99
1	Ciprofloxacin	Ramipril	SIC	82	41.0	0.99	0.66
2	Enalapril	Levofloxacin	SI	3	0.7	1.49	-0.56
2	Enalapril	Levofloxacin	SIC	31	19.9	0.63	0.08
3	Enalapril	Amoxicillin	SI	2	1.4	0.42	-2.20
3	Enalapril	Amoxicillin	SIC	21	15.2	0.45	-0.23
3	Enalapril	Azithromycin****	SIC	11	6.9	0.65	-0.33
3	Enalapril	Flucloxacillin****	SIC	3	6.6	-1.01	-

**suspected or interacting;*
***suspected, interacting or concomitant;*
****Ω_{025} >0, disproportionate reporting suggesting a drug-drug interaction;*
*****insufficient reports for suspected and interacting (SI) only.*

A potential mechanism for the observed interaction has not been identified. Most of the published reports summarised by Lomaestro indicate acute interstitial nephritis as the underlying cause of AKI with fluoroquinolones.[2] This is rare although the estimated incidence of 1 in 1,526 in the case control study of hospital admissions is likely to be an underestimate as patients may have been admitted with an alternative primary diagnosis or recovered before needing admission. Interstitial nephritis or other pathology due to a fluoroquinolone could be a trigger for ACE inhibitor-related AKI or more severe AKI leading to admission. There were no pathological descriptions in the VigiBase reports.

The case control study included only men as it was nested in a cohort study of the health of men aged 40 to 85 years.[1] The VigiBase case series included both males and females and the age range was similar or older. It included patients with risk factors for acute renal failure and risk factors for ACE inhibitor-related renal failure. It could be argued that these are sufficient in themselves to explain the AKI, but the addition of ciprofloxacin just prior to onset of AKI suggests that it may have had a causal or contributory role. Also the increased risks of AKI for fluoroquinolones with and without renin angiotensin blockers in the case-control study were estimated after adjusting for many of these risk factors.

At least half of the patients in the VigiBase series received ciprofloxacin together with enalapril in an ambulatory setting. This is also likely in the case-control study as the case patients were those admitted because of AKI. Therefore, co-prescription of enalapril and ciprofloxacin may not be uncommon in primary care. The US FDA has recently issued advice against using ciprofloxacin for specified urinary and respiratory infections, unless there are no alternatives, because of serious non-renal toxicities.[7] The observations in the VigiBase reports and case-control study[1] therefore need further investigation to ascertain if it is advisable to extend the advice to ciprofloxacin use with an ACE inhibitor because of an additional risk of nephrotoxicity in vulnerable patients.

The VigiBase reports also provide insights into the prescribing of ACE inhibitors and reiterate the need for careful consideration of age, renal function, hydration status and concomitant prescribing of diuretics or NSAIDs, and for monitoring throughout treatment for changes in clinical status that might increase the risk of renal impairment.

References

1. Bird ST, Etminan M, Brophy JM, Hartzema AG, Delaney JAC. Risk of acute kidney injury associated with the use of fluoroquinolones. CMAJ 2013;185: E475-E482.
2. Lomaestro BM. Fluoroquinolone-induced renal failure. Drug Saf. 2000;22:479-85.
3. Electronic Medicines Compendium: Summary of Product Characteristics for enalapril (Innovace®). Available from: https://www.medicines.org.uk/emc/medicine/1180. Accessed: 19 September 2016.
4. Drug consult: ACE inhibitor induced renal failure. Micromedex® Healthcare Series. [Online] Greenwood Village (Co): Thomson Micromedex. Available from: http://www.micromedexsolutions.com. Accessed: 21 November 2016.
5. Norén GN, Sundberg R, Bate A, Edwards IR. A statistical methodology for drug-drug interaction surveillance. Stat Med. 2008 Jul 20;27(16):3057-70.
6. US Food and Drug Administration: Product label for enalapril (Vasotec®). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/018998s080lbl.pdf. Accessed: 26 January 2017.
7. Electronic Medicines Compendium. Summary of Product Characteristics for ciprofloxacin. Available from: https://www.medicines.org.uk/emc/medicine/32450. Accessed: 19 September 2016.
8. US Food and Drug Administration: Product label for ciprofloxacin (Cipro®). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/019537s085,020780s042lbl.pdf. Accessed: 26 January 2017.

Desloratadine, loratadine and weight increase in children

Ermelinda Viola and Dr. Anita Conforti, Italy

Summary

In a signal detection screening focusing on paediatric patients, the association between desloratadine and weight increase was highlighted for children aged between 2 and 11 years. As desloratadine is a metabolite of loratadine, it was considered relevant to also include loratadine in the assessment. Loratadine and desloratadine are orally active, non-sedating, peripheral histamine 1 (H_1)-receptor antagonists used for the relief of the symptoms of seasonal allergic rhinitis, perennial allergic rhinitis and chronic idiopathic urticaria. Up to 6 November 2016, 44 reports of weight increase due to desloratadine and 115 to loratadine were submitted to the WHO global database of individual case safety reports, VigiBase. Among the reports of weight increase, 11 for desloratadine and 11 for loratadine were related to paediatric patients (<12 years old). The association of desloratadine and weight increase in children (2-11 years) reached a significant statistical value, unlike that of loratadine. Weight increase is not listed as an adverse reaction for either loratadine or desloratadine, but the reaction of 'increased appetite' is documented in the product information for both drugs. A plausible mechanism of loratadine and desloratadine-induced weight increase can be presumed, due to the action of these drugs on H_1- and H_3-receptors, which are mediators of energy intake. This analysis supports the possible association between loratadine, desloratadine and weight increase that, when affecting children, could have significant health consequences, including cardiovascular diseases (mainly heart disease and stroke), diabetes and musculoskeletal disorders.

Introduction

Loratadine and desloratadine are orally active, non-sedating, peripheral histamine 1 (H_1)-receptor antagonists used for the relief of the symptoms of seasonal allergic rhinitis, perennial allergic rhinitis and chronic idiopathic urticaria.[1,2] They belong to the newer second-generation H_1-antihistamines that bind to, but do not activate histamine receptors, thereby blocking the actions of histamine or histamine agonists. Compared with early (first-generation) ones, second-generation antihistamines have greater receptor specificity, are safer, cause less sedation, due to a lower penetration of the blood-brain barrier, and are more efficacious and less likely to cause drowsiness or psychomotor impairment.[3]

Loratadine was approved by the United States Food and Drug Administration in 1993, while desloratadine was authorized throughout the European Union (EU) and the United States (US) in 2001. Desloratadine is the primary active metabolite of loratadine (as of 2015 loratadine was available in many countries over the counter), and it is still subject to medical prescription.[4,5]

In the EU loratadine is approved for use in adults and children over the age of 2 years while desloratadine is approved for use in adults and children over the age of 1 year.[1,6] In the US desloratadine is approved for patients of 6 months and older.[7] The recommended daily dose of desloratadine for adults and adolescents (12 years and over) is 5 mg, for children from 6 to 11 years 2.5 mg, from 1 to 5 years 1.25 mg and from 6 to 11 months 1 mg, while the recommended daily dose for loratadine is 10 mg for adults and children above 12 years and children from 2 to 12 years are dosed by weight: 10 mg above 30 kg and 5 mg for body weight less than 30 kg.[1,6,7,8]

Loratadine and desloratadine achieve maximum plasma concentrations (Tmax) between 1-1.5 hours and 1.5-3.7 hours after administration, respectively. Increase in plasma concentrations of loratadine have been reported after concomitant use with ketoconazole, erythromycin, and cimetidine in controlled trials, but without clinically significant changes (including electrocardiographic). The enzyme responsible for the metabolism of desloratadine is still unknown and no clinically relevant interactions were observed in clinical trials with desloratadine tablets in which erythromycin or ketoconazole were co-administered.[1,6]

Weight increase takes place when body mass increases, as a result of fat deposits, additional muscle tissue, or excess fluid. It can have many alternative causes and can either derive from the increase of appetite, a range of diseases or be due to use of drugs that potentially influence the physiologic hormone levels.[9]

In a signal detection screening focusing on paediatric patients, the association between desloratadine and weight increase was highlighted for children aged between 2 and 11 years. As desloratadine is a metabolite of loratadine, it was considered relevant to also include loratadine in this assessment.

Reports in VigiBase

Loratadine

One hundred and fifteen reports concerning weight increase, obesity and appetite increased (WHO-ART preferred terms) were retrieved from the WHO global database of individual case safety reports, VigiBase as per 6 November 2016. In 97 reports loratadine is the sole suspect drug. The reports originate from 22 countries and concern 70 women and 33 men (in 12 cases the gender was unknown), aged between 4 to 77 years with a median age of 35 years. Among these reports 11 are related to children from 2 to 11 years, which are further described below.

Loratadine paediatric cases

Paediatric cases related to the use of loratadine are summarized in Table 1. Loratadine is the sole suspect drug in nine out of these eleven cases. Time to onset, where specified, varies from hours up to seven months. Two cases (3 and 4) reported other suspected drugs of which only cetirizine is known to cause weight gain.[10] In five cases the patient recovered. Cases 1, 2, 5, 9 and 11 reported a positive dechallenge. Case 10 reported a negative dechallenge. In case 1, a positive rechallenge was described concerning a 10-year-old male patient who increased his weight of at least 4 kg in one to two months after starting loratadine treatment two seasons in a row, and recovered when the drug was withdrawn.

The association of loratadine and weight increase did not reach a significant statistical value in children [IC -0.31; IC_{025} -2.41 for age group 2-11 years].

Desloratadine

Forty-four reports concerning weight increase, obesity and appetite increased (WHO-ART preferred terms) were retrieved from VigiBase on 6 November 2016, excluding two duplicates. In 34 reports desloratadine is the only suspected drug. The reports originate from 18 countries and concern 32 women and 11 men (in one case the gender was unknown), aged between 20 months and 60 years with a median age of 34.5 years. Among these reports 11 are related to children from 2 to 11 years, which are further described below.

Desloratadine paediatric cases

Paediatric cases related to the use of desloratadine are summarized in Table 2. Desloratadine is the sole suspect drug in five out these eleven cases. Time to onset varies from hours up to 20 months. In two cases (3 and 9) a positive dechallenge and a positive rechallenge was reported. Case 9 described a 7-year-old male patient who experienced rapid increase in appetite from the first day of treatment with desloratadine. He gained 4.5 kg in two months. Desloratadine was withdrawn, after which his appetite went back to normal and his weight decreased. The drug was later reintroduced, this time also leading to increased appetite, but the patient's weight was controlled with a diet.

In case 2 the presence of oedema could represent a possible alternative cause of weight gain. The onset of reaction occurred six days after desloratadine treatment was stopped. Four of the 11 children (cases 4, 5, 6 and 7) were concomitantly taking montelukast but the summary of product characteristics (SmPC) of this drug does not describe weight gain or increased appetite as adverse reactions.[11]

Case 7 describes also facial oedema and overdose during treatment with desloratadine and montelukast, but the reaction occurred twelve days after stopping the treatment with desloratadine. The patient's mother noticed development of a left facial oedema and weight gain of about 1 kg in one month, especially on abdominal circumference. The treatment with montelukast was also stopped and restarted. No rechallenge of the reactions was reported. The reporter felt that left facial oedema and weight gain were in direct relation with therapy with montelukast.

The association of desloratadine and weight increase reached a significant statistical value in children [IC 2.28; IC_{025} 0.32 for age group 2-11 years].

Literature and Labelling

Weight gain is not mentioned in the United Kingdom (UK) SmPCs of loratadine and desloratadine.[1,6] Although increased appetite is described in the UK SmPC for loratadine[1] with an incidence of 0.5%, it is not listed in the UK SmPC for desloratadine. The US product label for desloratadine lists increased appetite as an adverse event occurring more frequently with the drug than with placebo only for the age group 12-23 months.[7] The adverse effects of desloratadine were studied by the manufacturer in three placebo-controlled clinical trials of 246 children between 6 months and 11 years of age. Paediatric subjects aged 6 to 11 years received 2.5 mg once a day, subjects aged 1 to 5 years received 1.25 mg once a day, and subjects 6 to 11 months of age received 1.0 mg once a day. In the 6 to 11 year age group, no individual adverse event was reported by two percent or more of the subjects. In the 12 to 23 month age group, adverse events

Table 1. Case overview of paediatric reports in VigiBase of weight increase and appetite increased in association with loratadine

Case	Age/Sex	Other suspected (S) or concomitant (C) drugs	Reported reactions (WHO-ART)	Time to onset	Weight increase	Reporter qualification	Dechallenge/ Rechallenge	Outcome
1	10/M	-	Weight increase	Within 1 month	At least 4 kg in one to two months	Physician	Positive dechallenge/ Positive rechallenge	Recovered
2	7/M	Mometasone, clobetasone (both C)	Appetite increased, weight increase	Within 1 month	-	Physician	Positive dechallenge	Recovered
3	10/F	Beclometasone (S)	Puberty precocious, weight increase	-	-	Physician	Unknown	-
4	4/M	Cetirizine (S)	Hypersensitivity, weight increase	-	-	Other	Unknown	-
5	10/M	-	Agitation, appetite increased	Same day	-	Physician	Positive dechallenge	Recovered
6	8/M	-	Weight increase	1 month	4 kg in one month	Physician	Drug withdrawn	Unknown
7	10/F	Fluticasone (C)	Weight increase	7 months	5 kg above average	Physician, Pharmacist	-	-
8	8/F	Fluticasone (C)	Weight increase	7 months	5 kg above average	Physician, Pharmacist	-	-
9	8/M	-	Oedema pharynx, weight increase	-	-	Consumer	Positive dechallenge	Recovered
10	4/F	-	Appetite increased, weight increase	9 days	Had a weight of 30 kg after 2.5 years of treatment	Physician	Drug withdrawn	Not recovered
11	10/M	-	Thinking abnormal, weight increase	-	Excess weight more than 22%	Physician	Positive dechallenge	Recovered

Table 2. Case overview of paediatric reports in VigiBase of weight increase, obesity and appetite increased in association with desloratadine

Case	Age/Sex	Other suspected (S) or concomitant (C) drugs	Reported reactions (WHO-ART)	Time to onset	Weight increase	Reporter qualification	Dechallenge/ Rechallenge	Outcome
1	9/F	-	Weight increase	-	-	Physician	Unknown	-
2	10/F	Mometasone (S)	Oedema, weight increase	21 days	-	-	Drug withdrawn	-
3	10/F	-	Appetite increased, weight increase	14 days	-	Physician	Positive dechallenge/ Positive rechallenge	Recovered
4	6/M	Montelukast (S)	Abnormal weight gain*	12 months	-	Other Health Professional	Drug withdrawn	Unknown
5	6/F	Montelukast (S)	Abnormal weight gain*	9 months	-	Other Health Professional	Drug withdrawn	Unknown
6	7/M	Montelukast (S)	Abnormal weight gain*	20 months	-	Other Health Professional	Drug withdrawn	Unknown
7	4/M	Montelukast (S)	Face oedema, overdose, weight increase	12 days	1 kg in one month	Physician	Drug withdrawn	Not recovered
8	6/F	-	Weight increase	1 month	-	Consumer	Dose not changed	-
9	7/M	-	Appetite increased, weight increase	Same day	4.5 kg in two months	Pharmacist	Positive dechallenge/ Positive rechallenge	Recovered
10	8/F	Beclometasone/formoterol (S)	Weight increase	2 months	5 kg in six months	Consumer	Dose not changed	Recovering
11	11/F	-	Obesity	-	-	Other	-	Unknown

**Reported term*

reported for desloratadine and placebo in at least two percent of subjects receiving desloratadine syrup, and at a frequency greater than placebo, included appetite increased (3.1%, 1.6%).[7]

Moreover, in 2011 the Netherlands Pharmacovigilance Centre Lareb published a signal about desloratadine and increased appetite, describing three cases and concluding that an association was possible, due to similarity of desloratadine with loratadine.[12]

For other second-generation antihistamines, such as levocetirizine or cetirizine, weight gain is listed.[10,13]

In the literature, no information for desloratadine or loratadine and weight gain was found, but it is known that neuronal histamine and its receptors have been shown to regulate energy metabolism and are considered as anti-obesity targets. Several histamine receptor subtypes have been identified; of these, histamine H_1- and H_3-receptors have been specifically recognized as mediators of energy intake and expenditure.[14] This mechanism could probably represent a plausible explanation for weight gain due to antihistamines, even if second-generation H_1-antagonists, which include desloratadine, have high affinity and selectivity for the peripheral H_1-receptor. Specificity for the peripheral H_1-receptor site should avoid the potential for adverse effects on the central nervous system.[15]

Discussion and Conclusion

The review and analysis of all cases of weight increase, obesity and appetite increased for loratadine and desloratadine did not show that contributory factors such as concomitant drugs and or underlying disease were strong alternative explanations. These 115 cases for loratadine and 44 cases for desloratadine suggest that loratadine and desloratadine can increase weight, probably due to the increased appetite already documented in product information for loratadine and desloratadine, and children are affected as well as adults. Severe obesity in childhood is increasing in prevalence and is associated with considerable morbidity. Longitudinal cohort studies show that obesity during childhood is associated with medical comorbidity, and excess weight in childhood independently increases the risk of mortality related to the development of cardiovascular and metabolic disease in later life. It has also been linked with adverse effects on social, psychological, and academic development. Obese children are at a high risk of bullying, discrimination, lower health-related quality of life, and of impaired mental health. Drug therapies for children are limited, as is knowledge on their effect on weight and metabolism, so it is very important to detect any possible association between drugs and weight increase in paediatric patients. Weight gain reported among these cases, ranged between one and five kg, and rapid weight gain during infancy and early childhood may be a risk factor for general/abdominal obesity later in life.[16]

The UK SmPC of loratadine lists increased appetite as an undesirable effect, but the desloratadine data for increased appetite, that emerged also in a paediatric study conducted by the manufacturer, do not appear in the UK SmPC for desloratadine, but only in the US product label. VigiBase paediatric reports on weight increase with loratadine and desloratadine represent 22 cases with a supportive temporal relationship and a positive dechallenge in seven cases. Eleven out of the 22 paediatric cases had no other medication reported, while one case reported concomitant use of another antihistamine (cetirizine) and six cases mentioned corticosteroids (in one case dermatological products) previously associated with weight increase. The assessment of these reports suggests that desloratadine and loratadine could induce weight increase and the high proportion of paediatric reports (25%) for desloratadine suggests the possibility that use of this drug may contribute to childhood obesity. This assessment highlights the need for further evaluation of weight increase reports with desloratadine and loratadine. The association of desloratadine and the WHO-ART preferred term weight increase reached a significant statistical value in paediatric patients but not for loratadine; however, the statistical associations derived do not independently establish or rule out causality.

In conclusion, we consider weight increase with loratadine and desloratadine a signal that should be taken into a greater consideration when prescribing this medication to children.

References

1. Electronic Medicines Compendium: Summary of Product Characteristics for loratadine (Boots Hayfever Relief Instant-Melts). Available from: https://www.medicines.org.uk/emc/medicine/26058. Accessed: 20 March 2017.
2. Gupta S, Khalilieh S, Kantesaria B, Banfield C. Pharmacokinetics of desloratadine in children between 2 and 11 years of age. Br J Clin Pharmacol. 2007 May;63(5):534-40.

3. Church MK, Church DS. Pharmacology of antihistamines. Indian J Dermatol. 2013 May-Jun;58(3):219-24.
4. Hall SS. The Claritin Effect; Prescription for Profit. The New York Times. 2001 March 11 [cited 20 March 2017]. Available from: http://www.nytimes.com/2001/03/11/magazine/the-claritin-effect-prescription-for-profit.html.
5. Drugs.com - Desloratadine monograph. Available from: https://www.drugs.com/monograph/desloratadine.html. Accessed: 27 March 2017.
6. Electronic Medicines Compendium: Summary of Product Characteristics for desloratadine (Neoclarityn®). Available from: https://www.medicines.org.uk/emc/medicine/21616. Accessed: 20 March 2017.
7. DailyMed: Product label for desloratadine. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=6de2ba2e-dcfd-4efa-b24f-d6cbbe15e643. Accessed: 8 March 2017.
8. DailyMed: Product label for loratadine. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=660ac9df-f1b1-4c89-94dd-9fae0a013f3c. Accessed: 8 March 2017.
9. Nanri H, Shirasawa T, Ochiai H, Nomoto S, Hoshino H, Kokaze A. Rapid weight gain during infancy and early childhood is related to higher anthropometric measurements in preadolescence. Drug-induced weight gain. Drugs Today (Barc). 2005;41(8):547-55.
10. Electronic Medicines Compendium: Summary of Product Characteristics for cetirizine (Allacan®) Available from: https://www.medicines.org.uk/emc/medicine/30045. Accessed: 20 March 2017.
11. Electronic Medicines Compendium: Summary of Product Characteristics for montelukast. Available at https://www.medicines.org.uk/emc/medicine/32213. Accessed: 20 March 2017.
12. The Netherlands Pharmacovigilance Centre Lareb. Desloratadine and increased appetite. July 2011. Available from: http://www.lareb.nl/Signalen/kwb_2011_3_deslo.aspx. Accessed: 20 March 2017.
13. Levocetirizine dihydrochloride 5 mg film-coated tablets. Available at https://www.medicines.org.uk/emc/medicine/24190. Accessed: 20 March 2017.
14. Masaki T, Yoshimatsu H. Neuronal histamine and its receptors: implication of the pharmacological treatment of obesity. Curr Med Chem. 2010;17(36):4587-92.
15. Van Schoor J. Antihistamines: a brief review. Prof Nurs Today. 2012;16(5).
16. Coles N, Birken C, Hamilton J. Emerging treatments for severe obesity in children and adolescents. BMJ. 2016 Sep 29;354:i4116.

Ivermectin and serious neurological events

Rebecca E Chandler, Uppsala Monitoring Centre

Summary

Ivermectin is an anti-parasitic agent. It is indicated for use in the treatment of strongyloidiasis (*Strongyloides stercoralis*) and onchocerciasis (*Onchocerca volvulus*), but is also commonly used to treat scabies. Ivermectin is thought not to cross the blood-brain barrier in humans as it is excluded by a P-glycoprotein drug pump (mdr-1). Therefore, it has been considered to be free of the potential to cause neurological adverse drug reactions, except in situations of overdose. Serious neurological adverse events (SNAEs) were initially reported in public health programs in Africa to eliminate onchocerciasis through community-based ivermectin treatment. Cases of encephalopathy and coma were reported in Cameroon and the Democratic Republic of Congo in persons who concomitantly harbored high densities of another filarial species, *Loa loa*. Subsequent analyses revealed a correlation between pre-ivermectin treatment *Loa* microfilarial density and the risk of developing an SNAE. In VigiBase, the WHO global database of individual case safety reports, a report describing a case of encephalopathy with ivermectin from the Democratic Republic of Congo, which reported a lack of evidence of concomitant loaiasis, triggered a review of the database. This led to the identification of a case series of SNAEs occurring with the use of ivermectin outside the onchocerciasis indication. The occurrence of an SNAE after ivermectin may therefore not be entirely explained by concomitant onchocerciasis or loiasis infections. Knowledge of potential drug interactions and exploration of individual variations in the mdr-1 gene may be warranted to ensure safer use of ivermectin.

Introduction

Ivermectin is a member of the class of avermectins, which are highly active broad-spectrum, anti-parasitic agents. It is indicated for use in the treatment of strongyloidiasis (*Strongyloides stercoralis*) and onchocerciasis (*Onchocerca volvulus*); however, it is also commonly used to treat scabies, in circumstances such as immunocompromised patients, when topical therapy has failed, or institutionalized patients.[1,2] Ivermectin is not thought to readily cross the blood-brain barrier in humans, as it is excluded by a P-glycoprotein drug pump (mdr-1). Therefore, it has been considered to be free of the potential to cause neurological adverse drug reactions, except in situations of overdose.[3]

Serious neurological adverse events (SNAEs) were initially reported in public health programs in Africa to eliminate onchocerciasis through community-based ivermectin treatment; cases of encephalopathy and coma were reported in Cameroon and the Democratic Republic of Congo in persons who concomitantly harbored high densities of another filarial species, *Loa loa*. Subsequent analyses revealed a correlation between pre-ivermectin treatment *Loa* microfilarial density and the risk of developing an SNAE.[4,5]

In September 2015, a signal detection screening of VigiBase, the WHO global database of individual case safety reports, was performed focussing on drug-event combinations sensitive to reporting patterns mainly in Africa, Asia and Latin America and the Caribbean. During this screening a report for an SNAE (ataxia) from the Democratic Republic of the Congo was identified, which stated "This patient of 56-year old realises these conditions [encephalopathy]. It is very surprising to notice that there was no microfilariae in the calibrated thick blood smear." The lack of evidence of a high density of *L. loa* appeared to challenge the literature on SNAEs with ivermectin, and therefore it triggered a review of all SNAEs beyond the indication of use for onchocerciasis which could not be explained by concomitant infection with *L. loa*.

Reports in VigiBase

All reports for ivermectin received into VigiBase up to 27 November 2016 were identified for investigation. A total of 1,668 reports for ivermectin were identified. The most commonly reported adverse events (AEs) for ivermectin were pruritus (25.3%), headache (13.9%) and dizziness (7.5%).

Under the MedDRA System Organ Class "Neurological disorders" 426 reports were classified, and 156 of these were classified as "serious" according to ICH Guidance.[6] Of the serious reports, 60.9% (95) of them originated from Africa, 20.5% (32) from the Americas, 12.2% (19) from Europe, and 6.4% (10) from Asia. One duplicate report was identified and excluded from the analysis.

Sixty-four of the 155 serious reports described the use of ivermectin for *O. volvulus*. Forty-two did not include an indication; one reported only "infection parasitic". After clinical analysis, nineteen reports were excluded from this analysis: the reasons for exclusion

were neurological AEs reported in the context of other clinical syndromes (lactic acidosis/circulatory collapse, cerebral infarction/cerebral artery embolism, neuroleptic malignant syndrome, hepatitis/hepatic failure, brain cancer, pneumonia with hypotension, accidental exposure to product, sepsis complicating chemotherapy, multi-organ failure, history of epilepsy, Alzheimer's disease), topical ivermectin for rosacea, prolonged time to onset of ivermectin (8 years), and unclear onset of symptoms in relation to ivermectin.

The remaining 29 reports are included in this case series and were received from the United States, France, Japan, the Netherlands, Germany, Canada and Sierra Leone. The patient ages were mentioned in 25 reports and ranged from 11 to 97 years. Fifteen described males, 13 described females and the gender was not provided in one report.

Scabies was included an as indication in eleven reports, acarodermatitis in eight, filariasis due to *Wucheria bancrofti* in five, strongyloidiasis in three, taeniasis in one and myiasis in one. The time to onset of the SNAEs ranged from hours to 14 days, with 14 cases noting a time to onset of one day or less.

As seen in Table 1, examples of serious ADRs reported include unable to walk, consciousness disturbed or depressed level of consciousness or loss of consciousness, seizure or convulsion, encephalopathy or coma, and tremor.

The dosages of ivermectin ranged between 3 mg and 24 mg. Most of the cases reported a one-time dose or two doses separated by one week. Weight information was provided for the majority of cases, and there was no suggestion of overdose based on the data provided.

Nine reports documented a positive dechallenge, with resolution of symptoms after discontinuing ivermectin. One documented a positive rechallenge, with recurrence of symptoms with re-exposure on two occasions. Two patients died.

One case has been previously published, and documented the presence of ivermectin in brain tissue: "A 64-year-old male with a past medical history of giant cell arteritis, treated with prednisone developed sepsis, complicated by multisystem organ failure, after an aortic valve replacement. Sputum culture revealed S. stercoralis. A diagnosis of S. stercoralis hyperinfection syndrome was made; he was initiated on ivermectin 12 mg every 48 hours. He received three oral doses followed by two subcutaneous doses. In spite of clinical and microbiological improvement, the patient remained in a vegetative state and died on day 25. Autopsy revealed an elevated level of ivermectin in the brain tissue, 14 days after the last dose.".[7]

Literature and Labelling

The neurological events of dizziness (2.8%), somnolence (0.9%), vertigo (0.9%), and tremor (0.9%) were observed in human clinical trials for the treatment of strongyloidiasis, while drug-related headache (0.2%) was observed in trials for onchocerciasis; these events are included in the product label. Also included in the labelling is a warning for overdose which can manifest with headache, dizziness, asthenia, seizure, ataxia, and paresthesia.[1]

The label for ivermectin also provides the following warning: "Rarely, patients with onchocerciasis who are also heavily infected with *Loa loa* may develop a serious or even fatal encephalopathy either spontaneously or following treatment with an effective microfilaricide. In these patients, the following adverse experiences have also been reported: pain (including neck and back pain), red eye, conjunctival hemorrhage, dyspnea, urinary and/or fecal incontinence, difficulty in standing/walking, mental status changes, confusion, lethargy, stupor, seizures, or coma. This syndrome has been seen very rarely following the use of ivermectin. In individuals who warrant treatment with ivermectin for any reason and have had significant exposure to *Loa loa*-endemic areas of West or Central Africa, pre-treatment assessment for loiasis and careful post-treatment follow-up should be implemented.".[1]

Discussion and Conclusion

This case series describes SNAEs with the use of ivermectin beyond its indication for *O. volvulus*. Ivermectin acts by binding to glutamate-gated chloride ion channels which occur in invertebrate nerve and muscle cells; an increase in the permeability of the cell membrane results in paralysis and death of the parasite. It can also bind to mammalian GABA receptors and GABA-gated ion channels; however, neurotoxicity is prevented by the action of the P-glycoprotein drug pump (mdr-1) which limits penetration of the blood-brain barrier within the allowable dosage ranges for humans.[3]

It is well established in the veterinary world that certain breeds of dogs, such as collies, are sensitive to the neurotoxic effects of ivermectin; a loss of function in the mdr-1 gene in these breeds allows

for an accumulation of ivermectin within the brain.[8] Symptoms of neurotoxicity include lethargy, drooling, tremors/seizures, inability to stand, disorientation, coma.

Our data suggest that individuals may experience SNAEs outside the contexts of overdose and *L. loa* co-infection. While a number of AEs experienced by subjects in this case series are included in the product label (dizziness, headache, tremor), there were many other events which are similar to those described as neurotoxic effects as found in overdose or in susceptible dogs: coma, loss of consciousness/depressed level of consciousness, abasia and coma.

A number of cases included in the case series may be related to concomitantly administered drugs. Drugs that are substrates of CYP3A4 enzymes are often also substrates for P-glycoprotein transport, and thus there may be a risk of increased absorption past the blood-brain barrier with concomitant adminstration.[9] Several cases presented here reported concomitant use of such drugs, such as statins, HIV protease inhibitors, calcium channel blockers, and benzodiazepines. Current labelling for ivermectin contains no warning for co-administration with CYP3A4 substrates.

Another possible explanation is that some humans experiencing an SNAE after ivermectin therapy may also have mutations in the mdr-1 gene, allowing for penetration of ivermectin into the central nervous system. More than 50 naturally occurring single nucleotide polymorphisms (SNP) have been identified in the mdr-1 gene; the majority of these SNP are silent, and there is no current evidence of a mutation that results in loss of function. However, various combinations of these SNP, comprising different P-glycoprotein haplotypes, have been found to exhibit reduced mdr-1 expression.[10] Bourguinat *et al* performed a study in which they analysed mdr-1 genotypes in 13 subjects from Cameroon: four who experienced a serious adverse event and nine who did not. Haplotypes associated with altered drug disposition were present as homozygotes in two of the serious AE patients and in none of the control patients.[11] One of the cases in our series was investigated for the most common polymorphisms associated with decreased mdr-1 expression and found that none were present; however, further details were not provided.[8]

In conclusion, there is evidence that SNAEs can occur with ivermectin beyond the treatment of *O. volvulus* complicated by concomitant *L. loa* infection. Potential explanations include concomitantly administered drugs which inhibit CYP3A4 and polymorphisms in the mdr-1 gene. Consideration of changes to the product label to highlight potential drug interactions and explorations of polymorphisms in the mdr-1 gene may be desirable to ensure its safer use.

References

1. DailyMed: Product label for ivermectin (Stromectol®). Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=681888c9-af79-4b7d-ae80-c3f4f6f1effd. Accessed: November 2016.
2. Fawcett RS. Ivermectin use in scabies. Am Fam Physician. 2003;68(6):1089-92.
3. Schinkel AH, Smit JJM, van Tellingen O, Beijnen JH, Wagenaar E, van Deemter L et al. Disruption of the mouse mdr1a-p-glycopretin gene leads to a deficiency in the blood-brain barrier and to increased sensitivity to drugs. Cell 1994;77:491-502.
4. Boussinesq M, Gardon J, Gardon-Wendel N, Chippaw JP. Clinical picture, epidemiology, and outcome of Loa-associated serious adverse events related to mass ivermectin treatment of onchceriasis in Cameroon. Filiaria J. 2003; (Suppl 1): S4.
5. Gardon J, Gardon-Wendel N, Demanga-Ngangue Kamguo J, Chippaux JP, Boussinesq M. Serious reactions after mass treatment of onchocerciasis with ivermectin in an area endemic for Loa loa infections. Lancet 1997;350:18-22.
6. ICH Expert Working Group. Post-approval safety data management: definitions and standards for expedited reporting. 2003. Available from: https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2D/Step4/E2D_Guideline.pdf. Accessed: November 2016.
7. van Westerloo DJ, Landman GW, Prichard R, Lespine A, Visser LG. Persistent coma in Strongyloides hyperinfection syndrome associated with persistently increased ivermectin levels. Clin Infect Dis. 2014;58(1):143-4.
8. Mealey, KL, Bentjen SA, Gay JM, Cantor GH. Ivermectin sensitivity in collies is associated with a deletion mutation of the mdr1 gene. Pharmacogenetics. 2001;11:727-33.
9. Benet LZ, Cummins CL, Wu CY. Unmasking the dynamic interplay between efflux transporters and metabolic enzymes. Int J Pharm. 2004;277(1-2):3-9.
10. Macdonald N, Gledhill A. Potential impact of ABCB1 (p-glycoprotein) polymorphisms on avermectin toxicity in humans. Arch Toxicol. 2007;81:553.
11. Bourguinat C, Kamgno J, Boussinesq M, MacKenzie CD, Prichard R, Geary TG. Analysis of the mdr-1 gene in patients co-infected with Onchocerca volvulus and Loa loa who experienced a post-ivermectin serious adverse event. Am J Trop Med Hyg. 2010;83(1):28-32.

Table 1. Case series describing serious neurological adverse events after treatment with ivermectin beyond the onchocerciasis indication

Case	Age/Sex	Indication	Dose	Weight (kg)	Other suspect or concomitant medications	Reported terms	Time to onset	Additional info
1	18/M	Scabies infestation	15 mg, one dose	79	-	Lightheadedness, headache, unable to walk	1 day	Recovered in 24 hours Positive dechallenge
2	58/F	Acarodermatitis	12 mg, 1 per 1 day	60	Alprazolam, etizolam (both C)	Consciousness disturbed	0 days	Positive dechallenge
3	-/F	Myiasis	12 mg, 1 per 1 day	-	-	Seizure, off label use	-	Not recovered
4	51/M	Acarodermatitis	18 mg, 2 doses separated by one week	79	Pregabalin, lamotrigine, ariprazole, meloxicam, simvastatin, docusate (all C)	Abasia, aphasia, blindness, disease recurrence	-	Positive rechallenge
5	54/F	Acarodermatitis	-, 2 tablets, 2 doses separated by one week	68	-	Convulsion, local swelling, nausea, headache, heart rate increased, confusional state	-	-
6	32/F	Scabies	24 mg, one dose	109	-	Tremor, dizzy spells, mucosal dryness, abdominal pain lower	8 hours	-
7	81/F	Acarodermatitis	12 mg, 2 doses separated by one week	-	Digoxin, rebamipide, crotamiton, magnesium oxide, senna (all C)	Depressed level of consciousness, vomiting, asphyxia, pruritis aggravated, skin eruption	5 days after last dose	Died, 5 days after last dose from the events of depressed level of consciousness and asphyxia. Digoxin initiated 1 day prior to death.
8	11/F	Scabies	9 mg, one dose	40	-	Encephalopathy, coma, emesis	1 day	Recovered Positive dechallenge LP, EEG and MRI all performed
9	13/M	Scabies	1 DF*, 1 per 1 day	-	Piperonyl butoxide/ esdepallethrime (topical) (S)	Dizziness, crying abnormal, monoparesis, tremor, rigors, chills	10 hours	Recovered Positive dechallenge
10	47/F	Scabies	9 mg, 2 doses separated by one week	68	Piperonyl butoxide/ esdepallethrime (topical) (S)	Muscle weakness, hypoaesthesia, paraesthesia	7 days	Recovered
11	28/M	Scabies	18 mg, one dose	-	-	Confusional state, amnesia, malaise, emesis	1 day	Recovered; Similar symptoms reports twice in the past after ivermectin
12	68/M	Scabies	18 mg, one dose	-	-	Confusional state, disorder convulsive	14 days	Not recovered
13	33/M	Scabies	12 mg, one dose	65	Darunavir, ritonavir (both S)	Convulsions generalised	1 day	Recovered Positive dechallenge with all 3 drugs. Patient had started darunavir 12 months prior and ritonavir 8 days prior.
14	81/M	Scabies	3 mg, one dose on two days	-	-	Cerebellar syndrome, mental confusion, MRI abnormal	2 days	Drug withdrawn, no effect observed MRI abnormal 2 weeks after dosing

Case	Age/Sex	Indication	Dose	Weight (kg)	Other suspect or concomitant medications	Reported terms	Time to onset	Additional info
15	64/M	Strongyloidiasis	12 mg oral, then subcutaneous	57	-	Coma, neurotoxicity	-	Drug withdrawn, fatal outcome Therapy initiated for Strongyloides stercoralis infection in patient on prednisone for giant cell arteritis. Patient was s/p aortic valve replacement. Ivermectin levels measured in brain tissue at autopsy (30 ng/g). None of the most common polymorphisms in mdr-1 present
16	81/M	Acarodermatitis	9 mg, one dose	50	Rivastigmine, memantine, lornoxicam, troxipide (all C)	Tremor, pyrexia	0 days	Positive dechallenge
17	59/F	Strongyloidiasis Nematodiasis	21 mg, one dose on 2 days	100	Levothyroxine, olopatadine, vitamines, omega-3, melatonin, ascorbic acid, formoterol/budesonide, doxycycline, potassium citrate, pioglitazone, probiotics, vitamin D, prasterone, progesterone, colesevelam, montelukast, desvenlafaxine (all C)	Pain in jaw, tremor, chest pain, chills, back pain, tachycardia, dyspnoea, loss of consciousness, pain in extremity, thinking abnormal, peripheral coldness, hypersomnia, dizziness, asthenia, feeling abnormal, palpitations, paraesthesia, fatigue, blood potassium decreased, dysgeusia, constipation, muscle twitching, sedation, vertigo, sensation of heaviness, feeling cold, mood altered, feeling drunk, oropharyngeal pain, coxsackie virus test positive, inappropriate schedule of drug administration, orthostatic hypotension, neuralgia, affect lability, hypertension, asthma, confusional state, cough, nystagmus, headache, pyrexia, somnolence	1-2 days	Drug withdrawn, no effect observed
18	-/-	Acarodermatitis	-	-	Valproic acid, levetiracetam (both C)	Seizure, off label use	-	-
19	24/M	Scabies	3 mg, one dose	-	Oxatomide (S)	Confusion, convulsive disorder, cephalgia, fatigue, fall	0 days	Hospitalised, recovered
20	75/F	Taeniasis	6 mg	59	Lisinopril, amlodipine, metoprolol, clopidogrel (all C)	Asthenia, dizziness, dyspnoea, paraesthesia, vision decreased	0 days	Recovered with sequelae
21	-/M	Scabies infestation	12 mg	70	Ranitidine, amantidine, trazadone, lorazepam, haloperidol, toprimate, hydroxyzine, risperidone (all C)	Confusional state, unconsciousness	-	Hospitalised
22	-/M	Strongyloidiasis	18 mg, one dose on 2 days	86	-	Quality of life decreased, sleep disorder	-	-

Case	Age/Sex	Indication	Dose	Weight (kg)	Other suspect or concomitant medications	Reported terms	Time to onset	Additional info
23	56/F	Acarodermatitis	12 mg, one dose	55	Terbinafine (S) Dexlansoprazole, milnacipran, gabapentin, promethazine, meloxicam, trazadone, levothyroxine, propranolol, Lisinopril, predinose, azathioprine, diazepam, nortriptyline, lansoprazole, amoxicillin, furosemide, hydrochloroquine, vitamin D, vitamins (all C)	Aphasia, somatic delusion, abnormal faeces, alopecia, dry mouth, dyspnoea, ear infection, flushing, gastrointestinal motility disorder, headache, heart rate increased, lip swelling, musculoskeletal discomfort, oral discomfort, red blood cell count decreased, swollen tongue, urine colour abnormal, urine odour abnormal, weight decreased, white blood cell count decreased	2-5 days for aphasia and somatic delusion	Drug withdrawn, no effect observed
24	36/M	Filariasis due to Wuchereria bancrofti	12 mg, one dose	-	Albendazole (S)	Headache, vomiting, diarrhoea, abdominal discomfort	1 day	Recovered
25	43/F	Filariasis due to Wuchereria bancrofti	9 mg, one dose	-	Albendazole (S)	Headache, dizziness, vomiting	2 days	Recovered
26	11/F	Filariasis due to Wuchereria bancrofti	9 mg, one dose	-	Albendazole (S)	Headache, dizziness, vomiting	0 days	Recovered
27	28/M	Filariasis due to Wuchereria bancrofti	12 mg, one dose	-	Albendazole (S) Diclofenac, amoxicillin (both C)	Unconsciousness	0 days	Recovered Hospitalised 4 hours, gastric lavage
28	72/M	Filariasis due to Wuchereria bancrofti	12 mg, one dose	-	Albendazole (S)	Headache, abdominal discomfort, itching, vomiting, oedema	0 days	Recovered
29	97/F	Acarodermatitis	9 mg, 2 doses separated by one week	47	Febuxostat, furosemide, lansoprazole, sennoside a+b, magnesium oxide, carbocisteine, etizolam (all C)	Depressed level of consciousness, loss of consciousness, vomiting	6 days after 1st dose and 5 days after 2nd dose	Recovered Positive dechallenge

**DF = Dosage form*

Interaction between rosuvastatin and ticagrelor resulting in rhabdomyolysis

Dr. Viola Macolić Šarinić, Croatia

Summary

A potential signal of an interaction between ticagrelor and rosuvastatin leading to rhabdomyolysis is analysed. VigiBase, the WHO global database of individual case safety reports, contained five well-documented reports from five countries, with one very well-described case as a literature report. The patients who developed rhabdomyolysis were high-risk patients, namely elderly with initially an excessive dose of rosuvastatin, and two patients taking ezetimibe as concomitant therapy, which is known to raise rosuvastatin concentration by a factor of 1.2. The cases in VigiBase support the signal of an interaction between ticagrelor and rosuvastatin, especially in high-risk patients. One form of interaction is a worsening of the renal function caused by ticagrelor, resulting in the rise of plasma concentration of rosuvastatin, which then causes rhabdomyolysis. The other possibility, or additional type, can be the pharmacogenomics polymorphism and interaction on the level of the transporters, which can raise the rosuvastatin level. Patients who have developed elevated creatine kinase levels without clinical symptoms and patients with myositis who were also given this medication should be further assessed. If there is a plausible connection established, the possibility that this is indeed an adverse drug reaction as a consequence of an interaction between ticagrelor and rosuvastatin will be much higher.

Introduction

During a UMC signal detection screening in September 2016 focusing on drug-drug interactions, five unique cases were identified in the WHO global database of individual case safety reports, VigiBase, which indicated an interaction between ticagrelor and rosuvastatin resulting in rhabdomyolysis. Rhabdomyolysis (literally, "dissolution of skeletal muscle") is a syndrome caused by injury to skeletal muscle and involves leakage of large quantities of potentially toxic intracellular contents into plasma. The aetiology of rhabdomyolysis is trauma and muscle compression, infection, metabolic and genetic factors, but it can also be caused by certain drugs and mycotoxins. The multiplicity of potential causes of rhabdomyolysis notwithstanding, the common denominator appears to be disruption of the sarcolemma and release of intracellular myocyte components. In adults, the triad of muscle weakness, myalgias, and dark urine characterizes rhabdomyolysis. Myalgias and generalized muscle weakness are the most common presenting symptoms. Life-threatening renal failure and disseminated intravascular coagulation are serious complications that appear to be more common in adults. Sensitive laboratory markers of myocyte injury include elevated plasma creatine kinase (CK) levels (often more than four to five times above the normal limit).[1]

Ticagrelor, co-administered with acetylsalicylic acid, is indicated for the prevention of atherothrombotic events in adult patients with acute coronary syndromes or with a history of myocardial infarction and a high risk of developing an atherothrombotic event. Ticagrelor is a member of the chemical class cyclopentyltriazolopyrimidines, which is an oral, direct-acting, selective and reversibly-binding P2Y12 receptor antagonist, that prevents ADP-mediated P2Y12 dependent platelet activation and aggregation. Since platelets participate in the initiation and/or evolution of thrombotic complications of atherosclerotic disease, inhibition of platelet function has been shown to reduce the risk of cardiovascular events such as death, myocardial infarction or stroke. Ticagrelor also increases local endogenous adenosine levels by inhibiting the equilibrate nucleoside transporter.[1,2]

Rosuvastatin is indicated for the treatment of hypercholesterolemia in adults, adolescents, and children aged six years or older with primary hypercholesterolemia (type IIa including heterozygous familial hypercholesterolemia) or mixed dyslipidaemia (type IIb) as an adjunct to diet when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate. It is also indicated for homozygous familial hypercholesterolemia, as an adjunct to diet and other lipid lowering treatments (e.g. low-density lipoprotein (LDL) apheresis) or if such treatments are not appropriate. Another indication is the prevention of cardiovascular events in patients who are estimated to have a high risk for a first such event, as an adjunct to correction of other risk factors. Rosuvastatin is a selective and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor for cholesterol. The primary site of action of rosuvastatin is the liver, the target organ for lowe-

ring cholesterol. Rosuvastatin increases the number of hepatic LDL receptors on the cell surface, enhancing uptake and catabolism of LDL and it inhibits the hepatic synthesis of very-low-density lipoprotein (VLDL), thereby reducing the total number of VLDL and LDL particles.[3]

Rhabdomyolysis is a well-known adverse drug reaction (ADR) of statins, but for ticagrelor rhabdomyolysis is not listed as an ADR. An interaction between rosuvastatin and ticagrelor is not mentioned in the summary of product characteristics (SPCs) of either drug.[2,3]

Reports in VigiBase

As of 28 October 2016, VigiBase contained 16 reports with the reaction rhabdomyolysis (MedDRA preferred term) where the suspected medications were ticagrelor and rosuvastatin. The reports were received from five countries: the Netherlands (11 reports), Bulgaria (2), Canada (1), the United States (1) and Greece (1). The 11 reports from the Netherlands are in fact a single case. This was initially submitted in 2013 as a spontaneous ADR report from a physician. The other ten reports are the same case as the initial one, but from various companies as literature reports[4] of that Dutch case, and they are therefore duplicates. For the case report from

Table 1. Characteristics of case reports in VigiBase of rhabdomyolysis in association with ticagrelor and rosuvastatin interaction

Case	Age/Sex	Suspected (S), interacting (I) or concomitant (C) drugs	Daily dose	Reactions (MedDRA preferred terms)	Time to onset	Dechallenge/ Rechallenge	Outcome	Comment
1	76/F	Rosuvastatin, ticagrelor (both S) Ubidecarenone, pantoprazole, acetylsalicylic acid, fluticasone, formoterol, mometasone, salbutamol, ezetimibe, alfulozine, finasteride (all C)	10-40 mg 180 mg	Acute myocardial infarction, rhabdomyolysis, intentional product misuse	1 month	-/-	Unknown	No information about renal or liver function in medical history. The dose of rosuvastatin was increased around the time that ticagrelor was added. Unknown how long rosuvastatin was used before.
2	82/M	Rosuvastatin, ticagrelor (both I)	-	Drug interaction, rhabdomyolysis, acute kidney injury	-	-/-	Unknown	No information about renal or liver function in medical history.
3	70/M	Rosuvastatin, ticagrelor (both S)	20 mg 180 mg	Rhabdomyolysis	1.5 years after ticagrelor was added to therapy	Yes/-	Recovering	Medical history states hyperthyroidism. No information about renal or liver function in medical history. Patient had used rosuvastatin for many years without ADR. Ticagrelor was added 1.5 years before the elevated CPK (about 2000U/L) was noted.
4	46/M	Lisinopril, rosuvastatin, ticagrelor (all S) Oxycodone, hydrocodone (both C)	10 mg 20 mg 180 mg	Rhabdomyolysis, pain in extremity, walking disability, chest pain, myocardial infarction	1 month after ticagrelor was added to therapy	-/-	Unknown	Patient had been using rosuvastatin for 3 months when ticagrelor was added. Hospital admission due to symptoms. CK levels were between 800 and 1300 while in hospital. Treatment with fluids and CK levels returned to normal. Rosuvastatin was discontinued and ticagrelor and lisinopril were continued.
5	78/M	Rosuvastatin, ticagrelor (both S) Metoprolol, perindopril, omeprazole, ezetimibe (all C)	40mg 180 mg	Acute kidney injury, rhabdomyolysis	1 month after ticagrelor was added to therapy	Yes/-	Recovering	Patient had been using rosuvastatin for 6 years when ticagrelor was added. One week after introduction of tricagrelor, the renal function decreased from 60 ml/min to 52 ml/min. One month after introduction of ticagrelor, the patient developed acute renal failure after 6 days of vomiting and nausea, and developed rhabdomyolysis with an increase of CPK more than 10 000 IU/L.

Bulgaria a follow-up report was sent without any new information, so the second report is not counted as valid. Exclusion of these reports resulted in five unique cases, set out in Table 1.

The gender in four reports is male, and in one female. The case of the female patient (case 1) is doubtful, because of the question of whether the patient was actually a woman; she (he?) received as concomitant medications alfulozin and finasteride, which are indicated in the therapy of prostatic hypertrophy, also mentioned in the patient's medical history. It can be assumed that in this case the gender was wrongly stated, so all these cases concerned males.

In four of them, elderly patients were involved (70, 76, 78 and 82 years), and in one case a 46-year-old male patient experienced rhabdomyolysis, as reported by a physician. Two of the elderly males received the maximum daily dose of 40 mg of rosuvastatin, one received 20 mg, and for the fourth the dose is unknown; the younger patient received 20 mg of rosuvastatin daily. The recommended dose of ticagrelor is 90 mg twice a day. In two case reports the ticagrelor dose is not stated, but it can be assumed that the patients have received the standard dose, as this is the only recommended one. No report gives data about rosuvastatin plasma concentrations, and there is no data that could indicate that the drug concentrations were measured.

The status of the renal function of the patients were not captured or stated, except in the literature case where a rise of creatinine level was observed one week after the introduction of ticagrelor – from 108 to 124 micromole/l, which refers to a decrease in glomerular filtration from 60 ml/min to 52 ml/min. The recommendation for the rosuvastatin dose is that if the glomerular filtration is under 60 ml/min the dose should be 5 mg rosuvastatin a day, and this dose is recommended for patients older than 70 years, as higher doses are more frequently associated with ADRs. In these cases, none of the patients received only 5 mg rosuvastatin per day; instead, high doses were given (20 to 40 mg a day). For the 46-year-old patient the renal function is not recorded but he was taking lisinopril, an ACE inhibitor, which can also alter renal function.

Two patients used rosuvastatin and ezetimibe at the same time, which increases 1.2 times the AUC of rosuvastatin. Ezetimibe was given to the 72- and 76-year-old patients (cases 1 and 5), who were already taking the highest dose of rosuvastatin (40 mg). In the SPC for rosuvastatin this interaction is mentioned, but in the ezetimibe SPC it is stated that no clinically-significant pharmacokinetic interactions are found if ezetimibe and rosuvastatin are given together.[5]

In cases 3 and 5 the patient had used rosuvastatin for years without complaints at the time ticagrelor was added and after which the symptoms developed. In case 4 the patient had used rosuvastatin for three months when ticagrelor was introduced. The time to onset of the symptoms after start of the combination of rosuvastatin and ticagrelor was one month in three cases, 1.5 years in one case and in one case it is unknown. In the case where the time to onset is unknown only these two drugs are reported (no other concomitant therapy was listed).

Literature and Labelling

For rosuvastatin, cases of rhabdomyolysis were documented during clinical studies and in the post-authorisation phase. The frequency of rhabdomyolysis is described in the SPC of rosuvastatin as a rare ADR (in ≥1/10,000 to <1/1,000 patients). The risk factors for developing ADRs with rosuvastatin are to be an elderly patient (70 years and above) and/or to have renal and liver impairment. The development of the ADR relates to the blood concentration of rosuvastatin, as the higher the concentration, the more likely it is that the patient may develop rhabdomyolysis.[3]

In clinical studies, ticagrelor was commonly administered with statins, and evidence of a clinically significant adverse interaction was not observed.[2] For ticagrelor it was noted that in about 30% of treated patients, especially in those older than 75 years, creatinine levels increased (50% and more from the baseline level has been recorded). This is mentioned in the SPC section 4.4 – Special warnings and precautions for use, but worsening (impairment) of the renal function is not mentioned either in section 4.4, or as an ADR of ticagrelor in section 4.8.[2] It is not clear from the text if the renal impairment is because of the illness itself (cardiovascular), old age, or if it is a result of the use of ticagrelor, although it is recommended to check the renal function one month after initiating the treatment with ticagrelor. The SPC section 4.2 states that no dose adjustment for ticagrelor is needed in patients with renal impairment, as the primary route of elimination of the drug and its active metabolite is via hepatic metabolism (biliary secretion). In the elderly about 25% higher concentration of ticagrelor was found, but

with no clinically significant differences in comparison to younger patients. Caution is needed in patients with severe hepatic impairment[2], due to a higher possibility of bleeding.

Discussion and Conclusion

The cases identified in VigiBase are related to a possible interaction between the statin rosuvastatin and the platelet aggregation inhibitor ticagrelor, resulting in rhabdomyolysis as an ADR of rosuvastatin, which depends on the plasma concentration of the statin.

For ticagrelor, it is known from clinical studies that it can elevate the creatinine level and this is stated in section 4.4 of the SPC: Special warnings and precautions for use; it is recommended to measure the level of creatinine one month after the initiation of the ticagrelor therapy especially in patients over 75 years of age. In Section 4.8, as an ADR only higher creatinine levels are described but not renal impairment which can lead to some confusion for the prescriber, who cannot find renal impairment as an ADR of ticagrelor, but which is obvious if the creatinine level rises.

The theory behind this interaction is that ticagrelor alters the renal function, resulting in an increased rosuvastatin concentration which can then cause rhabdomyolysis when the critical concentration of rosuvastatin is reached. However, rosuvastatin is mainly eliminated by biliary excretion, with only 10% by renal excretion. Because of this, no general dose adjustment for rosuvastatin is suggested, only in patients with moderate and severe renal impairment. The patient described in the literature report, before he developed rhabdomyolysis, experienced nausea a few days after ticagrelor was introduced, which is a common ADR of this medicine. He vomited for six days, which precipitated acute renal failure, which then led to worsening of the renal failure with rising creatinine, thus causing rhabdomyolysis, which further impaired the renal function.

All patients described had risk factors for developing rhabdomyolysis, as the dose of rosuvastatin was already too high for their age and impaired renal function, and in two cases there was a possible interaction with ezetimibe, which in addition raises the rosuvastatin plasma concentration. Adding ticagrelor to this condition gave the additional hazard of increasing the rosuvastatin level to a critical one which caused the symptoms of rhabdomyolysis.

The cause of the rise of rosuvastatin concentration in combination with ticagrelor, is not only the raised creatinine level (which is the sign of renal impairment); genetic factors in the metabolism of ticagrelor and rosuvastatin should be taken into account. There is a possible interaction on the level of P-glycoprotein 1 (Pgp), as it has been shown that the digoxin level increases when given together with ticagrelor. The ticagrelor pharmacokinetics are influenced by three genetic loci: SLCO1B1, which codes OATP1B1 transporter activity, CYP3A4 (ticagrelor is also a mild inhibitor of that enzyme), and UGT2B7.[6] Ticagrelor is not metabolised by CYP2C9.[4] Rosuvastatin is not metabolised via the cytochrome P450, nor is it an inhibitor or inductor of these enzymes. Rosuvastatin is transported via OATP1B1 coded with the SLCO1B1 gene, the same as ticagrelor. If there is a gene polymorphism the concentration of rosuvastatin can rise.[2] Theoretically an addition of several genomic alterations could lead to ticagrelor – rosuvastatin interaction, which results in elevated rosuvastatin plasma concentrations, as we know that only 10% of rosuvastatin is eliminated by the kidneys: a genomic polymorphism on the level of Pgp could lead to an increased interaction on the level of Pgp and SLCO1B1. UGT2B7 is important for the metabolism of ticagrelor, which if altered could raise the concentration of ticagrelor, which could then have a higher interaction with rosuvastatin on the level of the transporters: a higher concentration of ticagrelor can interact on the level of Pgp and raise the level of rosuvastatin which can then lead to rhabdomyolysis.

In conclusion, in all cases a too-high dose of rosuvastatin was given to all patients initially – these doses are not recommended in this age group and in patients with impaired renal function. In two cases ezetimibe was given, despite this combination being known to raise rosuvastatin plasma levels. Ticagrelor raises the creatinine level, which appears not to have been checked in four of the patients one month after the introduction of the medicine, despite this being recommended in the SPC. The SPC for ticagrelor is misleading in that nowhere renal impairment is mentioned, but only the rise of creatinine level – which should be read indirectly as a worsening of the renal function after adding ticagrelor. For rosuvastatin it is not recommended to treat patients at all with severe renal impairment, and for moderate impairment a dose of 5 mg is recommended, even though only 10% of the medicine being excreted by the kidneys. In three cases a plausible time association can be found – the ADR appeared about one month after introduction

of the combination of these two medicines. After discontinuation of both medicines the symptoms regressed or disappeared. All patients were at a high risk of developing such a severe ADR, and the combination of rosuvastatin and ticagrelor taken in this high dose led in the end to the development of the symptoms – we can assume that the rosuvastatin concentrations were already high before adding ticagrelor which then rose to critical levels. The interaction may be caused not only by ticagrelor-related renal impairment, but also pharmacogenomics polymorphism which should be taken into account as it could lead to a higher concentration of rosuvastatin.

The reported cases can be seen as a signal for an interaction between ticagrelor and rosuvastatin especially in high-risk patients (elderly, renal impairment, pharmacogenomics polymorphism, interaction with ezetimibe). Cases of raised CK levels without clinical symptoms and patients with myopathy – myositis should also be studied to see if a combination between rosuvastatin and ticagrelor can lead to these ADRs.

References

1. Muscal E, DeGuzman MM. Medscape: Rhabdomyolysis. Jung LK (ed). New York (NY): Medscape. Accessed: January 2017.
2. European Medicines Agency: Summary of Product Characteristics for ticagrelor (Brilique®). Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001241/WC500100494.pdf Accessed: December 2016.
3. UK Medicines & Healthcare products Regulatory Agency: Summary of Product Characteristics for rosuvastatin. Available from: http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1486707217805.pdf Accessed: December 2016.
4. van Vuren AJ, Jong B, Bootsma HPR, van der Veen MJ, Feith G.W. Ticagrelor-induced renal failure leading to statin-induced rhabdomyolysis. The Netherlands Journal of Medicine. 2015(73);136-8.
5. UK Medicines & Healthcare products Regulatory Agency: Summary of Product Characteristics for ezetimibe. Available from: http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1463115553812.pdf Accessed: December 2016.
6. Varenhost C, Eriksson N, Johansson A, Barratt BJ, Hagstrom E, Akerblom A, et al.: on behalf of PLATO Investigators. Effect of genetic variations on ticagrelor plasma levels and clinical outcome. European Heart Journal. 2015(35);1901-12.

Ruxolitinib and peripheral neuropathy

Thomas Bradley, Uppsala Monitoring Centre and Sweden

Summary

Ruxolitinib is a selective Janus Associated Kinase (JAK) 1 and 2 inhibitor, which is at present indicated for myelofibrosis and polycythaemia vera. During a UMC signal detection screening in March 2016 the safety issue concerning axonal neuropathy in relation to ruxolitinib was noted. Literature shows that in patients treated with other JAK inhibitors peripheral neuropathy has been observed. In this review of 37 cases of ruxolitinib associated axonal and peripheral neuropathy reported to VigiBase, the WHO global database of individual case safety reports, we concluded that a causal association between ruxolitinib and peripheral neuropathy may exist, and represents a signal worth communicating so that stakeholders may act upon it.

Introduction

Ruxolitinib (INCB018424) is a selective inhibitor of the Janus Associated Kinases (JAKs) 1 and 2. These mediate the signalling of a number of cytokines and growth factors that are important for haematopoiesis and immune function.[1] Ruxolitinib has significant clinical benefits in patients with myelofibrosis by reducing spleen size, ameliorating debilitating myelofibrosis-related symptoms, and improving overall survival.[2] Ruxolitinib has also been demonstrated to be superior to standard therapy in controlling the hematocrit, reducing the spleen volume, and improving symptoms associated with polycythemia vera.[3]

In the United States, ruxolitinib is at present approved for treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis, as well as in patients with polycythemia vera who have had an inadequate response to, or are intolerant of, hydroxyurea.[4] In Europe also, ruxolitinib is authorized for myelofibrosis and polycythaemia vera, specifically for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis, as well as for the treatment of adult patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea.[1]

The most commonly reported adverse reactions in clinical trials were haematological, and the most frequent non-haematological reactions were bruising, dizziness, headache, constipation and herpes zoster. Serious bacterial, mycobacterial, fungal and viral infections, including progressive multifocal leukoencephalopathy, have occurred during treatment with ruxolitinib, and physicians are advised to carefully observe patients receiving ruxolitinib for signs and symptoms of infections, and to initiate appropriate treatment promptly.[1,4]

Peripheral neuropathy may be caused by a number of drugs and is one of the main reasons for patients to prematurely terminate antineoplastic treatment. Drug-induced peripheral neuropathies are often characterized by the development of a subacute or chronic, symmetrical polyneuropathy with a predominant sensory involvement.[5] Molecular mechanisms of drug-induced peripheral neuropathies have been addressed in several studies and a number of mechanisms have been postulated, including cytotoxic inflammatory changes, mitochondrial toxicity and enhanced oxidative stress, microtubular function disruption, voltage-gated ion channel dysfunction, functional impairment of ion channels of the transient receptor potential family, induction of neuronal apoptosis in dorsal root ganglia, demyelination, and reduction of VEGF neuro-protective action.[5]

During a UMC signal detection screening in March 2016 which focused on recently approved drugs and adverse events reported with a serious outcome, the safety issue concerning axonal neuropathy in relation to ruxolitinib was observed. For this review the scope was widened to peripheral neuropathy.

Reports in VigiBase

As of 21 March 2016, VigiBase, the WHO global database of individual case safety reports, had five reports where ruxolitinib was reported as suspected of causing axonal neuropathy (MedDRA preferred term), and 32 reports of neuropathy peripheral (MedDRA preferred term). Most of these reports originated from the United States (28); others came from Austria (2), France (2), Ireland (1), Greece (1), Italy (1), Slovenia (1) and the United Kingdom (1).

In all 37 reports ruxolitinib was reported as the sole suspect drug. In 29 of them ruxolitinib was used for the indication myelofibrosis, in three cases the indication was polycythaemia, in one case the indication was lymphatic disorder and in four the indication was

unknown. Twenty of the 37 cases were reported by a physician. Among the 36 reports where information on gender was provided, 19 patients were female and 17 patients male. The median age was 72 years (range 49 to 91 years).

Time to onset ranged from seven days up to three years. Information on outcome was provided in 15 reports and included five with no recovery where the action for ruxolitinib is unknown. In two cases there was no recovery after a dose reduction of ruxolitinib and in one the patient was recovering after dose reduction. The remaining cases included four negative dechallenges and three positive dechallenges. One positive dechallenge case had the restart of ruxolitinib in a lower dose, with an unknown outcome. In another positive dechallenge case, atorvastatin, which is a rare cause of peripheral neuropathy,[6] was withdrawn at the same time as ruxolitinib.

A review of concomitant drugs identified three cases where drugs known to be a common cause of peripheral neuropathy were reported (hydroxycarbamide in two reports and tacrolimus in one).[7,8] In four cases HMG-CoA-reductase inhibitors (simvastatin and atorvastatin), and in one bezafibrate, were reported as concomitant drugs. These are known to possibly cause peripheral neuropathy in rare cases.[9,10]

Reviewing the medical history identified two cases where the patient had previously used drugs known to cause peripheral neuropathy, namely hydroxycarbamide in one report and thalidomide in the other. In the second case, it its known that the patient experienced peripheral neuropathy while using thalidomide but information is lacking on action taken with thalidomide and outcome of neuropathy. Another case mentions that the patient was on chemotherapy (bortezomib) when the peripheral neuropathy occurred and that ruxolitinib was used before and after the chemotherapy.

Literature and Labelling

Neuropathy is not described in current ruxolitinib drug labels[1,4] and no literature reports on peripheral neuropathy have been found for ruxolitinib.

Discussion and Conclusion

Peripheral neuropathy is a common adverse effect of several chemotherapeutic agents such as taxanes, platinum agents, vinca alkaloids, thalidomide, and bortezomib, a proteasome inhibitor. No single mechanism explaining the peripheral neuropathy has been identified and the precise pathophysiology remains complex.[11] A number of mechanisms for drug-induced peripheral neuropathy have been postulated, including immune-based demyelination.[5]

In clinical trials there was at least one case of peripheral neuropathy potentially related to ruxolitinib among the 39 patients in the essential thrombocythemia cohort in an ongoing phase 2 study.[12,13]

Of these 37 cases on ruxolitinib suspected to cause peripheral neuropathy in VigiBase, it is not possible to draw any conclusions regarding a possible mechanism, but it should be noted that other immunomodulatory drugs such as TNFα blocking molecules may cause peripheral neuropathy via demyelination.[5]

For some other JAK inhibitors, peripheral neuropathy has been commonly observed. At one institution, treatment-emergent peripheral neuropathy was documented in 44 of 100 myelofibrosis patients treated with the JAK1/2 inhibitor momelotinib,[14] and with XL019, a selective JAK2 inhibitor, peripheral neuropathy was observed in seven out of nine patients in a phase 1 trial.[15] This substance was also used in a study of 30 patients with myelofibrosis where central and/or peripheral neurotoxicity (including later onset of classical "glove and stocking" sensory peripheral neuropathy) developed in all patients, leading to termination of the study.[16]

In the present case series, there were two cases with obvious indications of significant confounding, namely the case where the patient experienced peripheral neuropathy while using thalidomide and the case where the patient was on chemotherapy when the peripheral neuropathy occurred. Among the other 35 reports there were medicines with known potential to cause peripheral neuropathy listed in eight reports. In none of them, however, were these drugs reported as suspected, and five of these drugs were lipid lowering agents, commonly used in this elderly population.

In light of a possible class effect and a possible mechanism, these cases constitute a signal of peripheral neuropathy induced by ruxolitinib, and this merits further investigation to assess the need for updating relevant product information.

References

1. European Medicines Agency: Summary of Product Characteristics for ruxolitinib (Jakavi®). Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002464/WC500133223.pdf. Accessed: 9 November 2016.
2. Verstovsek S, Mesa RA, Gotlib J, Levy RS, Gupta V, Dipersio JF, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. N Engl J Med. 2012;366:799-807.
3. Vannucchi AM, Kiladjian JJ, Griesshammer M, Masszi T, Durrant S, Passamonti F, et al. Ruxolitinib versus standard therapy for the treatment of polycythemia vera. N Engl J Med. 2015;372:426-35.
4. Dailymed: Product label for ruxolitinib (Jakafi®). Available from https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=f1c82580-87ae-11e0-bc84-0002a5d5c51b&type=display. Accessed: 9 November 2016.
5. Diezi M, Buclin T, Kuntzer T. Toxic and drug-induced peripheral neuropathies: updates on causes, mechanisms and management. Curr Opin Neurol. 2013 Oct;26(5):481-8.
6. Electronic Medicines Compendium: Summary of Product Characteristics for atorvastatin (Lipitor®). Available from: https://www.medicines.org.uk/emc/medicine/28526. Accessed: 9 November 2016.
7. Electronic Medicines Compendium: Summary of Product Characteristics for hydroxycarbamide (Hydrea®). Available from: https://www.medicines.org.uk/emc/medicine/19081. Accessed: 9 November 2016.
8. Electronic Medicines Compendium: Summary of Product Characteristics for tacrolimus (Prograf®). Available from: https://www.medicines.org.uk/emc/medicine/11102. Accessed: 9 November 2016.
9. Electronic Medicines Compendium: Summary of Product Characteristics for simvastatin (Zocor®). Available from: http://www.medicines.org.uk/emc/medicine/1201. Accessed: 9 November 2016.
10. Electronic Medicines Compendium: Summary of Product Characteristics for bezafibrate (Bezalip®). Available from: http://www.medicines.org.uk/emc/medicine/20856. Accessed: 9 November 2016.
11. Addington J, Freimer M. Chemotherapy-induced peripheral neuropathy: an update on the current understanding. F1000Research. 2016;5:F1000 Faculty Rev-1466.
12. ClinicalTrials.gov: An Open-Label Study to Determine the Safety and Efficacy of INCB018424 in Patients with Advanced Polycythemia Vera or Essential Thrombocythemia Refractory to Hydroxyurea (Identifier NCT00726232). Available from: https://clinicaltrials.gov/ct2/show/NCT00726232. Accessed: 1 December 2016.
13. Verstovsek S, Passamonti F, Rambaldi A, Barosi G, Rosen PJ, Levy R, et al. Durable Responses with the JAK1/ JAK2 Inhibitor, INCB018424, In Patients with Polycythemia Vera (PV) and Essential Thrombocythemia (ET) Refractory or Intolerant to Hydroxyurea (HU). Blood (ASH Annual Meeting Abstracts) 2010;116(21):313.
14. Abdelrahman RA, Begna KH, Al-Kali A, Hogan WJ, Litzow MR., Pardanani A, et al. Momelotinib treatment-emergent neuropathy: prevalence, risk factors and outcome in 100 patients with myelofibrosis. Br J Haematol. 2015;169:77-80.
15. Shah NP, Olszynski P, Sokol L, Verstovsek S, Hoffman R, List AF, et al. A phase I study of XL019, a selective JAK2 inhibitor, in patients with primary myelofibrosis, post-polycythemia vera, or post-essential thrombocythemia myelofibrosis. Blood (ASH Annual Meeting Abstracts) 2008;112(11):98.
16. Verstovsek S, Tam CS, Wadleigh M, Sokol L, Smith CC, Bui LA, et al. Phase I evaluation of XL019, an oral, potent, and selective JAK2 inhibitor. Leuk Res. 2014 Mar;38(3):316-22.

Response from Novartis

Background

This document provides Novartis' comment on the draft of "Ruxolitinib and peripheral neuropathy" which concluded that a causal association between ruxolitinib and peripheral neuropathy may exist and which will be published in Signal from UMC – WHO Collaborating Centre for International Drug Monitoring.

Peripheral neuropathy was fully evaluated as a potential signal in the Jakavi (ruxolitinib) PSUR 5 (23 Aug 2014 – 22 Feb 2015) based on a literature report[1] describing treatment-emergent peripheral neuropathy (TE-PN) with momelotinib (a JAK-1/2 inhibitor that also targets TYK2[2]). As a result of evaluating peripheral neuropathy and discussing it with health authorities, it was ultimately concluded that at this time, peripheral neuropathy does not constitute an important potential risk and should be continued to be monitored as part of routine pharmacovigilance activities for ruxolitinib.

The evaluation of ruxolitinib does not support the hypothesis that peripheral neuropathy is class-related, as the kinase selectivity and pharmacological profile of other JAK inhibitors differs from that of ruxolitinib, e.g. due to inhibition of non-JAK family kinases. For instance, momelotinib, originally described as a selective JAK1/2 inhibitor, is also a potent TBK1/IKKε inhibitor (IC_{50}=58 nM and 42 nM, respectively).[3] In contrast, ruxolitinib fails to inhibit TBK1 or IKKε in this assay (IC_{50} >1 μM for both).

Two other JAK inhibitors were associated with neurotoxicity which resulted in termination of further clinical development. The first one, XL019, a highly selective JAK2 inhibitor was associated with central and/or peripheral neurotoxicity in all patients. Since neurotoxicity, particularly CNS neurotoxicity has been rare or absent in studies of other JAK2 inhibitors and its almost universal occurrence with XL019, suggests likely an undefined, off target effect.[4] Another potent selective JAK 1/2 inhibitor, AZD 1480, was associated with low grade neurotoxicity that was considered unacceptable in long term therapy.[5]

In addition, there was a single literature report of a distal symmetric polyneuropathy in a patient treated with tofacitinib (Xeljanz), a JAK1/3 inhibitor for rheumatoid arthritis.[6]

Epidemiology

Neurological manifestations including peripheral neuropathy have been reported with myeloproliferative neoplasms. Peripheral neuropathy in patients with polycythemia vera was explained with the underlying mechanism of hypoxia due to increased blood viscosity and abnormal platelet aggregation associated with the disease.[7,8,9] In a report from Kawasaki Y *et al.*[10] neurological disturbance of the lower extremities was seen in a patient due to extramedullary hematopoietic mass complicated with primary myelofibrosis. In a study that reviewed 28 patients with a PV diagnosis, 11 experienced paresthesia. In 13 (46%) patients, clinical examination revealed features suggesting polyneuropathy. Nerve conduction indexes were abnormal in 20 (71%) patients, suggesting the presence of a predominantly sensory axonal polyneuropathy.

No literature reports of peripheral neuropathy linked to ruxolitinib were retrieved.

Data from interventional trials

There were no clear differences in the incidence rates of peripheral neuropathy (narrow SMQ) observed in the randomized periods in the two phase III studies in myelofibrosis (Study CINCB18424-351 and Study CINC424A2352) and polycythemia vera (CINC424B2301 and CINC424B2401). In MF, the incidence was 3% in ruxolitinib arm vs 2.2% in control arms. In PV, in the incidence was 2.7% in ruxolitinib arm vs. 3.2% in control arm.

In longer term follow-up in both MF and PV, exposure-adjusted analysis showed no disproportionate increase in frequency with prolonged exposure.

Data from the safety database

Novartis global safety database was searched cumulatively through 22 Feb 2017, with the following PTs: Neuropathy peripheral/Polyneuropathy/Peripheral motor neuropathy/Peripheral sensorimotor neuropathy/Peripheral sensory neuropathy/Axonal neuropathy and retrieved 103 cases (with 107 events). Of these, in 42 cases, the event was confounded by medical conditions (such as pre-existing neuropathy, diabetes mellitus, thyroid disorder) and concomitant medications (such as statins, thalidomide and its anologues) which are either associated with or can lead to neuropathy. In five cases, due to implausible temporal relationship or negative rechallenge, the role of ruxolitinib in relation to the events was unlikely. In 55 cases, limited information precluded complete medical assessment. In the remaining case, due to positive dechallenge and absence of strong explanation, the role of ruxolitinib in polyneuropathy was considered possible.

Disproportionality analysis

Traditional safety signal detection activities for all marketed products (both, multinational and mono-national) are supported by a data mining tool, the Empirica Signal System™ (ESS) applied to the Novartis safety database. The disproportionality analyses use the MGPS (Multi-Item Gamma Poisson Shrinker) statistical algorithm and statistical hits are considered when the lower limit of the confidence interval (EB05) is greater than 2. Quantitative analysis using Novartis safety database in the Empirica signal system was performed for peripheral neuropathy and did not reveal a technical signal (defined as EB05>2), with a maximal EB05 of 1.487 through March 2017.

Conclusions

At this time, it is not possible for the sponsor to conclude that peripheral neuropathy is caused by JAK inhibition based on the currently available clinical trial and postmarketing safety data coupled with the known mechanistic data of ruxolitinib. However, the MAH agrees with UMC and will continue monitoring peripheral neuropathy by applying routine pharmacovigilance as well as data mining technologies. The safety topic will be presented again, should future data indicate causality.

References

1. Abdelrahman RA, Begna KH, Al-Kali A, Hogan WJ, Litzow MR, Pardanani A, et al (2015). Momelotinib treatment-emergent neuropathy: prevalence, risk factors and outcome in 100 patients with myelofibrosis. Br J Haematol. 2015 Apr; 169(1):77-80.
2. Tyner JW, Bumm TG, Deininger J, Wood L, Aichberger KJ, Loriaux MM, et al (2010). CYT387, a novel JAK2 inhibitor, induces hematologic responsesnand normalizes inflammatory cytokines in murine myeloproliferative neoplasms. Blood. 2010 Jun 24;115(25):5232-40.
3. Zhu Z, Aref AR, Cohoon TJ, Barbie TU, Imamura Y, Yang S et al (2014). Inhibition of KRAS-driven tumorigenicity by interruption of an autocrine cytokine circuit. Cancer Discov. 2014 Apr; 4(4):452-65.
4. Verstovsek S, Tam CS, Wadleigh M, Sokol L, Smith CC, Bui LA et al (2014). Phase I evaluation of XL019, an oral, potent, and selective JAK2 inhibitor. Leuk Res. 2014 Mar;38(3):316-22.
5. Verstovsek S, Hoffman R, Mascarenhas J, Soria JC, Bahleda R, McCoon P et al (2015). A phase I, open-label, multi-center study of the JAK2 inhibitor AZD1480 in patients with myelofibrosis. Leuk Res. 2015 Feb;39(2):157-63.
6. Zeidler C, von Köckritz A, Luger TA, Ständer S, Husstedt IW, Tsianakas (2015) A J Eur Acad Dermatol Venereol. 2015 Mar. Tofacitinib, a novel JAK3 inhibitor, as a potential cause of distal symmetric polyneuropathy.
7. Wollina U (2015). Burning feet in polycythemia vera - peripheral sensorimotor axonal neuropathy with erythromelalgia. Int J Gen Med. 2015 Feb 2; 8:69-71.
8. Poza JJ, Cobo AM, Martí-Massó JF. Peripheral neuropathy associated with polycythemia vera. Neurologia. 1996 Oct;11(8):276-9.
9. Mihalj M, Titlić M, Bonacin D, Dogaš Z. Sensomotor axonal peripheral neuropathy as a first complication of polycythemia rubra vera: A report of 3 cases. Am J Case Rep. 2013;14:385-7.
10. Kawasaki Y, Nakazora T, Suzukawa M, Tominaga T, Wang ZK, Shinohara K (2010). Neurological disturbance of the lower extremities by an extramedullary hematopoietic mass complicated with primary myelofibrosis. The Japanese journal of clinical hematology. 2010 May;51(5):349-52.

Dasabuvir and ritonavir/ombitasvir/paritaprevir and decompensation of hepatic cirrhosis and hepatorenal syndrome

The signal text was published in SIGNAL October 2016

Response from AbbVie

Summary

An analysis of clinical, post marketing and literature data did not establish a causal association between 2-DAA (ombitasvir/paritaprevir/ritonavir) or 3-DAA (ombitasvir/paritaprevir/ritonavir and dasabuvir) therapy and Hepatorenal syndrome (HRS). Reported cases of HRS reflected occurrence as part of the natural history of chronic HCV infection including a complication of cirrhosis, especially in individuals with ascites and other predisposing comorbidities.

Introduction

HCV infection causes a wide spectrum of clinical consequences including chronic hepatitis, cirrhosis, hepatocellular carcinoma, and extrahepatic manifestations, e.g., chronic kidney diseases. Hepatorenal syndrome (HRS) is defined as functional renal impairment that occurs in patients with advanced liver cirrhosis, fulminant liver injury, or hepatitis.[1] It is characterized by increased renal vasoconstriction, a reduced glomerular filtration rate (GFR), subsequent rise in creatinine, and impaired sodium and water excretion in the absence of renal pathology.[1]

Paritaprevir is a nonstructural protein 3/4A (NS3/4A) protease inhibitor co-administered with the pharmacokinetic enhancer ritonavir. Ombitasvir is a NS5A inhibitor, and dasabuvir is a NS5B polymerase inhibitor. In both US and EU, the 3 direct acting antiviral (3-DAA) regimen (ombitasvir/paritaprevir/ritonavir and dasabuvir) is approved for the treatment of HCV genotype 1 infection, and the 2-DAA regimen (ombitasvir/paritaprevir/ritonavir) is approved for the treatment of HCV genotype 4 infection. Pharmacokinetic studies have demonstrated that renal impairment does not result in clinically meaningful changes in exposures for any of the components of the 2DAA or 3-DAA regimens. As a result these regimens are included in US and EU guidelines for treatment of patients with renal insufficiency, including patients on dialysis.

The current evaluation assessed whether 2-DAA and 3-DAA regimens contributed to the occurrence of HRS when administered according to the product label.

Methodology and Results

AbbVie's clinical database (through July 2016) and global safety database (through 04 November 2016) were searched for any reports coincident with 2-DAA or 3-DAA using the MedDRA v19.0 Preferred Terms (PTs) consistent with the UMC analysis: Hepatorenal syndrome, Acute hepatic failure, Acute kidney injury, Encephalopathy, Hepatic encephalopathy, Acute renal injury, Chronic kidney disease, Hyperkalaemia, Hyponatraemia, Renal failure, or Renal impairment.

Retrieved reports were considered in-scope for analysis if the report included the PT of Hepatorenal syndrome or at least 1 hepatic adverse event (PT of Acute hepatic failure, Encephalopathy, or Hepatic encephalopathy) and at least 1 renal adverse event (PT of Acute kidney injury, Acute renal injury, Chronic kidney disease, Hyperkalaemia, Hyponatremia, Renal failure, or Renal impairment). A total of 43 reports were included in the current analysis. Of these 43 reports, the majority (34 reports) involved concomitant use of ribavirin which can increase risk of HRS by inducing hemolytic anemia and reducing renal oxygen supply. Individuals with concomitant ribavirin use also had other confounding factors for renal disease, including a history of hypertension, diabetes, stroke, or cardiovascular disease.

The remaining 9 reports without concomitant ribavirin use contained other confounding factors for renal disease, i.e., hypertension (3 reports); cryoglobulinemic glomerulonephritis secondary to HCV (1 report); infections including C. difficile, spontaneous bacterial peritonitis, or infection in the dialysis catheter (3 reports); end stage of hepatic metastases of pancreatic carcinoma with liver and kidney failure, cardiovascular disease (1 report); and rhabdomyolysis (1 report).

A medical history of cirrhosis was observed in 86% (37/43) of the reports, with 26 reports containing Child-Pugh (CP) scores (CP A: 12 reports, CP B: 10 reports, CP B/C: 1 report, and CP C: 3 reports). In addition, 65% (28/43) of all reports in the current analysis had medical history of more advanced cirrhosis evidenced by portal hypertension (5); ascites or esophageal varices (4 each); thrombocytopenia, concomitant use

of spironolactone, or Child-Pugh B score (3 each); coagulopathy or hepatic decompensation (2 each); and hepatic hydrothorax or portal vein thrombosis (1 each), prior to treatment initiation.

Review of literature was conducted and did not identify any reports of HRS for 2-DAA or 3-DAA regimens.

Discussion and Conclusion

HRS occurs as part of the natural history of HCV infection and has been reported as a common complication of cirrhosis, especially in individuals with ascites.[1,2] In the current analysis, 86% (37/43) of the reports were in patients with HCV related cirrhosis and 65% (28/43) of reports had features of more advanced cirrhosis e.g., portal hypertension, ascites prior to treatment with 2-DAA or 3-DAA. Portal hypertension causes fluid and albumin accumulation into the peritoneal cavity resulting in ascites and reduces effective circulatory volume which may contribute to renal dysfunction. Cases of hepatic decompensation have been identified with 2-DAA or 3-DAA regimens. The product labels contain relevant information on these cases, including guidance on the management of cirrhotic patients receiving these regimens. The 2 or 3-DAA regimens are not recommended in moderate (Child-Pugh B) and are contraindicated in severe (ChildPugh C) hepatic impairment as stated in the company's labeling for both products. Four reports included in the current analysis had pretreatment severe (Child-Pugh C) cirrhosis indicating off-label use.

HCV related cirrhosis has been associated with insulin resistance, diabetes mellitus, and dyslipidemia, which are also major risk factors for renal disease.[2] HCV infection also leads to deposition of cryoglobulins and other immune complexes in the mesangium leading to glomerulonephritis.[2] All cases retrieved by the current search criteria were either confounded by risk factors or had primary alternative etiologies for the reported events. Confounding factors included cryoglobulinemic vasculitis, cryoglobulinemic glomerulonephritis secondary to HCV, diabetes, hypertension, stroke, infections e.g., spontaneous bacterial peritonitis, co-administration with ribavirin (causing hemolytic anemia) and autoimmune anemia.

In conclusion, the current cumulative analysis of clinical, postmarketing and literature data did not establish a causal association between 2-DAA or 3-DAA therapy and HRS at this time. Reported cases of HRS reflected occurrence as part of the natural history of chronic HCV infection including a complication of cirrhosis, especially in individuals with ascites and other predisposing comorbidities.

References

1. Shah N, et al. Hepatorenal syndrome. Disease-a-Month. 10// 2016; 62(10):364375.
2. Azmi AN, et al. Hepatitis C and kidney disease: an overview and approach to management. World J Hepatol. 2015;7(1):78-92.

The UMC Measures of Disproportionate Reporting

A brief guide to their interpretation

The Information Component (IC)

The Information Component (IC), originally introduced through the BCPNN (Bayesian Confidence Propagation Neural Network), is a measure of the disproportionality between the observed and the expected reporting of a drug-ADR pair. A positive IC value indicates that a particular drug-ADR pair is reported more often than expected, based on all the reports in the database. Similarly, a negative IC value means that the drug-ADR pair is reported less frequently than expected. The higher the value of the IC, the more the combination stands out from the background.

The IC value is solely calculated from:

- the total number of reports in the database (N_{tot})
- the total number of reports on the ADR term (N_{adr})
- the number of reports on the drug (N_{drug}), and
- the total number of reports on the specific drug-ADR pair (N_{comb}).

New reports may cause the IC to either increase or decrease. When the IC is calculated from large numbers, a new report is less likely to cause a major fluctuation in the IC value. The IC_{025} value is the lower limit of a 95% credibility interval for the IC. The credibility interval provides information about the stability of a particular IC value: the narrower the interval, the higher the stability.

The IC does not imply causality of a potential adverse reaction caused by a drug. The IC shows the quantitative dependency between the ADR and the drug based on the reporting to the WHO International Database of Suspected Adverse Drug Reactions.

If the IC value increases over time and the IC_{025} value is positive, this is suggestive of a connection between the drug and the adverse reaction. However, as alternative explanations for the positive IC need to be considered, clinical assessment remains essential in the identification of a signal.

Omega (Ω)

Omega (Ω) is, just as the IC, a measure of disproportionate reporting, however not for a drug-ADR pair but for a drug-drug-ADR triplet. The purpose of Ω is to detect potential signals of drug-drug interactions.

For Ω, the expected reporting on a drug-drug-ADR triplet is based on a model where both drugs add to the baseline risk of the ADR, independently of each other. A positive Ω indicates that the two drugs, when used together, increase the risk of the ADR more than the sum of the risks attributable to each drug separately.

Ω is calculated based on the following information:

- the relative reporting rate of the ADR for reports listing neither of the drugs (f_{00})
- the relative reporting rate of the ADR for reports listing drug 1 but not drug 2 (f_{10})
- the relative reporting rate of the ADR for reports listing drug 2 but not drug 1 (f_{01}), and
- the relative reporting rate of the ADR for reports listing both drugs (f_{11}).

As the IC, Ω may fluctuate over time as new reports enter the database. Also like the IC, each Ω comes with a 95% credibility interval, whose lower limit is denoted Ω_{025}. Ω does not imply causality of a potential drug-drug interaction. It is a quantitative measure of the deviation in reporting on the drug-drug-ADR triplet relative to a baseline model where the drugs are assumed to independently add to the baseline risk of the ADR.

If Ω increases over time and Ω_{025} is positive, this is suggestive of a drug-drug interaction, based on the reporting to the WHO International Database of Suspected Adverse Drug Reactions. However, as alternative explanations for the positive Ω need to be considered, clinical assessment of the case series is essential in the identification of an interaction signal.

References:

1. Bate A, Lindquist M, Edwards IR, Olsson S, Orre R, Lansner A, De Freitas RM. A Bayesian neural network method for adverse drug reaction signal generation. Eur J Clin Pharmacol. 1998 Jun;54(4):315-21.
2. Norén GN, Hopstadius J, Bate A. Shrinkage observed-to-expected ratios for robust and transparent large-scale pattern discovery. Stat Methods Med Res. Feb 2013;22(1):57-69.
3. Norén GN, Sundberg R, Bate A, Edwards IR. A statistical methodology for drug-drug interaction surveillance. Stat Med. 2008 Jul 20;27(16):3057-70. DOI: 10.1002/sim.3247.

For more information, please contact:
Uppsala Monitoring Centre, Box 1051, SE-751 40 Uppsala, Sweden. E-mail: info@who-umc.org

Caveat Document

Accompanying statement to data released from VigiBase, the WHO international database of suspected adverse drug reactions

Uppsala Monitoring Centre (UMC) in its role as the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring receives reports of suspected adverse reactions to medicinal products from National Centres in countries participating in the WHO pharmacovigilance network, the WHO Programme for International Drug Monitoring (PIDM). The information is stored in VigiBase, the WHO international database of suspected adverse drug reactions (ADRs). It is important to understand the limitations and qualifications that apply to this information and its use.

The reports submitted to UMC generally describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. In most instances it cannot be proven that a specific medicinal product (rather than, for example, underlying illness or other concomitant medication) is the cause of an event.

Reports submitted to National Centres come from both regulated and voluntary sources. Some National Centres accept reports only from medical practitioners; other National Centres accept reports from a broader range of reporters, including patients. Some National Centres include reports from pharmaceutical companies in the information submitted to UMC; other National Centres do not.

The volume of reports for a particular medicinal product may be influenced by the extent of use of the product, publicity, the nature of the reactions and other factors. No information is provided on the number of patients exposed to the product.

Some National Centres that contribute information to VigiBase make an assessment of the likelihood that a medicinal product caused the suspected reaction, while others do not. Time from receipt of a report by a National Centre until submission to UMC varies from country to country. Information obtained from UMC may therefore differ from those obtained directly from National Centres.

If in doubt or in need of help for interpretation of country specific data, UMC recommends to contact the concerned NC before using the data.

For the above reasons interpretations of adverse reaction data, and particularly those based on comparisons between medicinal products, may be misleading. The supplied data come from a variety of sources. The likelihood of a causal relationship is not the same in all reports. Any use of this information must take these factors into account.

Confidential data

According to WHO policy and UMC Guidelines, ADR reports sent from the WHO PIDM member countries to VigiBase are anonymized, but they are still to be considered sensitive due to the nature of the data.

When receiving and using adverse reaction data ("Data"), the user agrees and acknowledges that it will be the controller of any such Data. Accordingly, the user shall adhere to all applicable legislation such as, but not limited to, EU and national legislation regarding protection of personal data (e.g. the Data Protection Directive 95/46/EC and Regulation (EC) No 45/2001, as applicable). Transfer of sensitive data to a third party is generally prohibited subject to limited exceptions explicitly stated in applicable legislation.

As the controller of the Data, the user shall be liable for any and all processing of the Data and shall indemnify and hold the UMC harmless against any claim from a data subject or any other person or entity due to a breach of any legislation or other regulation regarding the processing of the Data.

Non-permitted use of VigiBase Data includes, but is not limited to:

- patient identification or patient targeting
- identification, profiling or targeting of general practitioners or practice

Any publication, in whole or in part, of information obtained from UMC must include a statement:
(i) regarding the source of the information

(ii) that the information comes from a variety of sources, and the likelihood that the suspected adverse reaction is drug-related is not the same in all cases,

(iii) that the information does not represent the opinion of the World Health Organization.

Omission of this statement may exclude the responsible person or organization from receiving further information from VigiBase.

UMC may, in its sole discretion, provide further instructions to the user, responsible person and/or organization in addition to those specified in this statement and the user, responsible person and/or organization undertakes to comply with all such instructions.

Uppsala Monitoring Centre

WHO Collaborating Centre for
International Drug Monitoring
P.O. Box 1051, SE-751 40, Uppsala, Sweden
Tel +46 18 65 60 60, Fax +46 18 65 60 88
Visiting adress: Bredgränd 7, Uppsala
E-mail: info@who-umc.org
Internet: www.who-umc.org